Exhibit 12c

CONSUMER PROMOTIONAL SPENDING RANK BY CORPORATION

1999 Rank	Corporation	YTD 11/99 Share (%)
1	Glaxo Wellcome	12
2	Schering-Plough	12
3	Pfizer	11
4	Merck & Co.	10
5	AstraZeneca	9
6	Johnson & Johnson	6
7	Aventis	4
8	American Home Products	4
9	Warner-Lambert	4
10	SmithKline Beecham	4

Source: IMS HEALTH, Integrated Share of Voice and Competitive Media Reporting

Performance Indicator: The direct-to-consumer spend is estimated nationally across 11 monitored media including TV, magazines, newspapers, radio and other.

Exhibit 13a

JOURNAL ADVERTISING SPEND BY CORPORATION

1998 Rank	1999 Rank	Corporation	1999 Spend ($000)	% Change Over 1998
2	1	AstraZeneca	52,180	31
1	2	Pfizer	46,622	-25
3	3	Merck & Co.	30,972	-2
5	4	Aventis	28,832	24
7	5	Forest Labs	20,995	-4
6	6	American Home Products	19,995	-11
16	7	Searle	19,553	65
8	8	Johnson & Johnson	19,126	-3
17	9	Hoffmann-La Roche	13,357	14
9	10	Lilly	12,020	-35
		TOTAL MARKET	470,435	-5

Sources: Integrated Promotional Services™, National Journal Audit

Performance Indicator: The journal advertising spend represents the cost of advertising in medical journals.

ment for atrial fibrillation/flutter, was scheduled to be launched during the first quarter of 2000, while Zeldox, an anti-psychotic, is awaiting FDA approval. Finally, the impending merger with Warner-Lambert will certainly have an effect on next year's rankings.

Other highlights include:

- Warner-Lambert climbed from 11th to eighth due primarily to the sustained success of Lipitor. In addition, Neurontin (classified as a treatment for seizure disorders) realized a staggering 76-percent growth, due to its popularity in treating other neurological conditions, such as bipolar disorder and diabetic neuropathy. These two products are responsible for two-thirds of the company's prescription sales.
- With the powerful launch of Celebrex, Searle enjoyed an astronomical growth rate of 92 percent and also climbed two rungs to 17th place.
- Hoffmann-La Roche remained in 15th place despite the addition of $263 million from sales of three new products — Roche's Xenical, an anti-obesity drug introduced in April; Tamiflu, an anti-flu product that hit the market in November; and Genentech's Herceptin, a cytostatic that was launched in October 1998.

Prescriptions

The top-20 companies remained intact, except that Searle entered the arena, forcing Abbott into the 21st slot (see Exhibit 11, p. 54).

- American Home Products retained leadership with a 5.8 percent share, augmenting its 1998 tally by 2.8 million prescriptions. Premarin and Prempro, two of the top-20 products, accounted for 43 percent of the company's scripts, with a significant contribution from Effexor XR (a specific neurotransmitter modulator).
- Bristol-Myers Squibb, with a 5.5 percent share, began closing in on the leader. Driven by the strong performances of Glucophage and Plavix, Bristol added 8.3 million prescriptions to last year's total for a six-percent increase, after only one-percent growth in 1998.
- Pfizer barely squeaked by Novartis, jumping two notches to third place, and boasts the highest increase in the industry — 19.8 million scripts. Pfizer has three products among the top 20, accounting for about half of its total prescription activity.
- Warner-Lambert grew 22 percent, which gave it a script increase of 15 million, 13 million of which are attributable to Lipitor.
- The launch of Celebrex was a shot in the arm for Searle, boosting it into the top 20. The company grew by 54 percent, especially significant in light of the fact that five of its top-ten products suffered double-digit declines in 1999.

continued on page 60

Exhibit 13b

JOURNAL ADVERTISING SPEND RANK BY PRODUCT

1998 Rank	1999 Rank	Product	Manufacturer	1999 Spend ($000)	% Change Over 1998
14	1	Atacand	AstraZeneca	16,653	167
10	2	Celexa	Forest	13,773	96
NA	3	Celebrex	Searle	11,593	NA
3	4	Norvasc	Pfizer	11,214	2
8	5	Prozac	Lilly	8,161	3
15	6	Prevacid	Tap	7,757	29
63	7	Plendil	AstraZeneca	7,674	247
NA	8	Vioxx	Merck & Co.	7,069	NA
74	9	Allegra	Aventis	6,951	262
1	10	Trovan	Pfizer	6,611	-55
		TOTAL MARKET		470,435	-5

Sources: Integrated Promotional Services™, National Journal Audit

Performance Indicator: The journal advertising spend represents the cost of advertising in medical journals.

Exhibit 14a

OFFICE AND HOSPITAL PROMOTIONAL SPEND RANK BY CORPORATION

1998 Rank	1999 Rank	Corporation	1999 Spend ($000)	% Change Over 1998
1	1	Pfizer	471,144	12
5	2	Merck & Co.	291,412	29
2	3	Glaxo Wellcome	238,264	-8
3	4	Bristol-Myers Squibb	229,040	-11
7	5	Johnson & Johnson	225,982	15
9	6	Schering-Plough	218,008	13
10	7	Aventis	207,836	10
6	8	AstraZeneca	204,500	2
4	9	SmithKline Beecham	190,974	-16
8	10	American Home Products	188,039	-4
		TOTAL MARKET	4,319,629	7

Sources: Integrated Promotional Services™, Office & Hospital Promotion Reports

Performance Indicator: The contact spend represents the cost of detailing office and hospital-based physicians.

Promotional spending

Total promotional spending (Detailing, Sampling, and Advertising) totaled $12.8 billion from January through November 1999 (see Exhibit 12, p. 56). Direct-to-Consumer advertising (DTC) continued to have an increasing presence in the pharmaceutical industry. For year-to-date November 1999, DTC spend reached $1.6 billion for both branded and unbranded advertising. This represents a 29-percent increase over the same time period last year. Overall, DTC promotions accounted for 12.8 percent of audited promotional spend. Leading products and corporations using DTC are highlighted in Exhibit 12b and 12c, p. 56 and 58, respectively.

The greatest increase in DTC advertising was seen in the television category, with pharmaceutical companies spending 47 percent more than in 1998. Sixty percent of the industry's spend for DTC was television ads ($985.0 million). The rest of the DTC spend is primarily comprised of print ads. With $638.4 million spent for print ads, this represented 39 percent of the industry spend for DTC. The remaining one percent is attributed to radio and outdoor advertising.

After two consecutive years of double-digit annual growth for professional promotional expenditures, the U.S. pharmaceutical industry exhibited a more modest increase in spending this year. Less resources were allocated to professional journal advertising, totaling $470 million in 1999. This is a five-percent decline compared to 1998. The top corporations accounted for 58 percent of the industry professional journal expenditures (see Exhibit 13a and 13b, p. 58 and 60, respectively). The top products advertised to physicians in medical journals were AstraZeneca's Atacand, Forest's Celexa, and Searle's Celebrex.

Sampling accounted for $6.7 billion, representing 60 percent of the total professional promotional expenditure. In addition to the sampling, $4.3 billion[3] was spent on office and hospital-based physician contacts, representing a moderate seven-percent increase over 1998 (see Exhibit 14a, left; 14b and 15, p. 62). □

REFERENCES

1. *Integrated Promotional Services*™ provides information to examine and evaluate pharmaceutical promotional efforts, including the efforts of competitors. *Office Promotion Reports* can be used to analyze promotional activity direct to office-based physicians by value, cost, quality, and effectiveness. *Total Sampling Report* examines the entire pharmaceutical sampling picture, and *Hospital Promotion Reports* provide insight on the volume, cost, quality, and effectiveness of promotions by pharmaceutical sales representatives to hospital-based physicians.

2. *National Prescription Audit Plus (NPA), Mail Order Prescription Audit*™ measures dispensed prescriptions from non-government mail order pharmacy services, including Retired Persons Services, Medco, and more.

3 Represents promotional expenditures for office-based and hospital-based physician contacts and journal advertising.

continued on page 62

WHAT TO WATCH FOR IN 2000

- **Mergers/Acquisitions:** Taking advantage of synergies to increase profitability and promotional strength.
- **Competition:** With less than a share point's difference within the top five companies, the race for first place is sure to intensify.
- **Drug Utilization:** Continued volume increases as successful products become more deeply entrenched and economic growth continues.
- **Global Branding:** Watch for companies to concentrate on specific disease states to gain larger market share within a therapeutic class.
- **New Products:** A resurgence of product launches that meet the needs and desires of aging baby boomers and a growing elderly population.
- **Pipeline Investments:** Further spending in quality of life drugs as well as treatments for hypertension, asthma, diabetes, and cancer.
- **Politics:** The upcoming presidential election is likely to have an effect on the healthcare system in 2000 and beyond.

Exhibit 14b

OFFICE AND HOSPITAL PROMOTIONAL SPEND BY PRODUCT

1998 Rank	1999 Rank	Product	Manufacturer	1999 Spend ($000)	% Change Over 1998
NA	1	Celebrex	Searle	147,187	NA
NA	2	Vioxx	Merck & Co.	74,665	NA
9	3	Zithromax	Pfizer	66,066	31
24	4	Allegra	Aventis	65,986	82
4	5	Lipitor	Warner-Lambert	64,497	10
5	6	Prozac	Eli Lilly	60,172	17
15	7	Claritin	Schering-Plough	58,740	32
2	8	Biaxin	Abbott	58,679	-11
11	9	Prevacid	Tap	58,568	15
3	10	Augmentin	SmithKline Beecham	55,219	-12
		TOTAL MARKET		4,319,629	7

Sources: *Integrated Promotional Services™, Office & Hospital Promotion Reports*

Performance Indicator: The contacts measure represents the number of times a detail was performed with office and hospital-based physicians. The contact spend represents the cost of detailing office and hospital-based physicians.

Exhibit 15

TOTAL PROFESSIONAL SPEND RANK BY MANUFACTURER

1998 Rank	1999 Rank	Corporation	1999 Spend ($000)	% Change Over 1998
1	1	Pfizer	517,766	7
4	2	Merck	322,383	25
5	3	AstraZeneca	256,680	6.5
3	4	Glaxo Wellcome	246,382	-8
8	5	Johnson & Johnson	245,108	14
2	6	Bristol-Myers Squibb	239,501	-16
9	7	Aventis	236,667	11.24
10	8	Schering-Plough	229,616	9
7	9	American Home Products	208,034	-4
6	10	SmithKline Beecham	202,658	-13

Sources: *Integrated Promotional Services™, Office & Hospital Promotion Reports, and National Journal Audit*

Performance Indicator: The contact spend represents the cost of detailing office and hospital-based physicians. The journal advertising spend represents the cost of advertising in medical journals.

3. *National Disease and Therapeutic Index* ™ provides information about the patterns and treatment of disease encountered in office-based practice in the continental U.S. Patient visits are recorded by diagnosis, drug therapy, and patient demographics.

4. *New Product Spectra*™ provides pertinent launch information from seven IMS core services. Extracting the sales, prescription, promotion, pricing, and trial usage data for 265 major pharmaceutical launches. *NPS* is a Windows-based software application designed to provide insight on key launch success factors.

5. *NPA Plus*™ provides weekly and monthly views of the prescription marketplace. Prescribed and dispensed information can be analyzed by channel of distribution, physician specialty, substitution patterns, and covers all products methods of payments, therapy classes, and manufacturers.

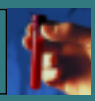
6. *Retail Perspective*™ and *Provider Perspective*™ provide monthly purchase activity of chain, independent, food store and mail order pharmacies, non-federal hospitals, federal facilities, clinics, closed-wall HMOs and long-term care facilities. Dollar volume, unit volume, and average price across distribution channels can be analyzed for all products, therapy classes, and manufacturers.

7. *DTC Integrated Share of Voice Report* provides quantitative assessments of promotional spend to professional and consumers. IMS HEALTH DTC advertising is reported via a joint licensing agreement with Competitive Media Reporting.

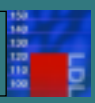
8. *The National Arthritis Foundation* web site: www.arthritis.org

High Blood Cholesterol

Detection



Evaluation



Treatment

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on

Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Executive Summary

NATIONAL INSTITUTES OF HEALTH
NATIONAL HEART, LUNG, AND BLOOD INSTITUTE
DJA-1169

Discrimination Prohibited: Under provisions of applicable public laws enacted by Congress since 1964, no person in the United States shall, on the grounds of race, color, national origin, handicap, or age, be excluded from participation in, be denied the benefits of, or be subjected to discrimination under any program or activity (or, on the basis of sex, with respect to any education program or activity) receiving Federal financial assistance. In addition, Executive Order 11141 prohibits discrimination on the basis of age by contractors and subcontractors in the performance of Federal contracts, and Executive Order 11246 states that no federally funded contractor may discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin. Therefore, the National Heart, Lung, and Blood Institute must be operated in compliance with these laws and Executive Orders.

High Blood Cholesterol

Detection

Evaluation

Treatment

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on

Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Executive Summary

National Cholesterol Education Program

National Heart, Lung, and Blood Institute

National Institutes of Health

NIH Publication No. 01-3670
May 2001

Acknowledgements

National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Members:
Scott M. Grundy, M.D., Ph.D. – Chair of the Panel
Diane Becker, R.N., M.P.H., Sc.D.
Luther T. Clark, M.D.
Richard S. Cooper, M.D.
Margo A. Denke, M.D.
Wm. James Howard, M.D.
Donald B. Hunninghake, M.D.
D. Roger Illingworth, M.D., Ph.D.
Russell V. Luepker, M.D., M.S.
Patrick McBride, M.D., M.P.H.
James M. McKenney, Pharm.D.
Richard C. Pasternak, M.D., F.A.C.C.
Neil J. Stone, M.D.
Linda Van Horn, Ph.D, R.D.

Ex-officio Members:
H. Bryan Brewer, Jr., M.D.
James I. Cleeman, M.D. – Executive Director of the Panel
Nancy D. Ernst, Ph.D., R.D.
David Gordon, M.D., Ph.D.
Daniel Levy, M.D.
Basil Rifkind, M.D.
Jacques E. Rossouw, M.D.
Peter Savage, M.D.

Consultants:
Steven M. Haffner, M.D.
David G. Orloff, M.D.
Michael A. Proschan, Ph.D.
J. Sanford Schwartz, M.D.
Christopher T. Sempos, Ph.D.

Staff:
Susan T. Shero, R.N., M.S.
Elaine Z. Murray

Executive Committee Liaison and Reviewers of the Full Report

Executive Committee Liaison to the Panel:
Stephen Havas, M.D., M.P.H., M.S.

Reviewers of the Full Report of ATP III:
Eugene Braunwald, M.D., W. Virgil Brown, M.D., Alan Chait, M.D., James E. Dalen, M.D., Valentin Fuster, M.D., Ph.D., Henry N. Ginsberg, M.D., Antonio M. Gotto, M.D., D.Phil., Ronald M. Krauss, M.D., John C. LaRosa, M.D., F.A.C.P., Thomas H. Lee, Jr., M.D., Linda Meyers, Ph.D., Michael Newman, M.D., Thomas Pearson, M.D., Ph.D., Daniel J. Rader, M.D., Frank M. Sacks, M.D., Ernst J. Schaefer, M.D., Sheldon G. Sheps, M.D., Lynn A. Smaha, M.D., Ph.D., Sidney C. Smith, Jr., M.D., Jeremiah Stamler, M.D., Daniel Steinberg, M.D., Ph.D., Nanette K. Wenger, M.D.

National Cholesterol Education Program Coordinating Committee

The *Third Report of the National Cholesterol Education Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults* was approved by the National Cholesterol Education Program Coordinating Committee, which comprises the following organizational representatives:

Member Organizations

National Heart, Lung, and Blood Institute
Claude Lenfant, M.D. (Chair)
James I. Cleeman, M.D. (Coordinator)

American Academy of Family Physicians
Theodore G. Ganiats, M.D.

American Academy of Insurance Medicine
Gary Graham, M.D.

American Academy of Pediatrics
Ronald E. Kleinman, M.D.

American Association of Occupational Health Nurses
Pamela Hixon, B.S.N., R.N., C.O.H.N-S

American College of Cardiology
Richard C. Pasternak, M.D., F.A.C.C.

American College of Chest Physicians
Gerald T. Gau, M.D.

American College of Nutrition
Harry Preuss, M.D.

American College of Obstetricians and Gynecologists
Thomas C. Peng, M.D.

American College of Occupational and Environmental Medicine
Ruth Ann Jordan, M.D.

American College of Preventive Medicine
Lewis H. Kuller, M.D., Dr.P.H.

American Diabetes Association, Inc.
Alan J. Garber, M.D., Ph.D.

American Dietetic Association
Linda Van Horn, Ph.D., R.D.

American Heart Association
Scott M. Grundy, M.D., Ph.D.

American Hospital Association
Sandra Cornett, R.N., Ph.D.

American Medical Association
Yank D. Coble, Jr., M.D.

American Nurses Association
To be named

American Osteopathic Association
Michael Clearfield, D.O.

American Pharmaceutical Association
James M. McKenney, Pharm.D.

American Public Health Association
Stephen Havas, M.D., M.P.H., M.S.

American Red Cross
Donald Vardell, M.S.

Association of Black Cardiologists
Karol Watson, M.D., Ph.D.

Association of State and Territorial Health Officials
Joanne Mitten, M.H.E.

Citizens for Public Action on Blood Pressure and Cholesterol, Inc.
Gerald J. Wilson, M.A., M.B.A.

National Black Nurses Association, Inc.
Linda Burnes-Bolton, Dr.P.H., R.N., M.S.N., F.A.A.N.

National Medical Association
Luther T. Clark, M.D.

Society for Nutrition Education
Darlene Lansing, M.P.H., R.D.

Society for Public Health Education
Donald O. Fedder, Dr.P.H., M.P.H.

Associate Member Organization

American Association of Office Nurses
Joyce Logan

Federal Agencies

NHLBI Ad Hoc Committee on Minority Populations
Yvonne L. Bronner, Sc.D., R.D., L.D.

Agency for Healthcare Research and Quality
Francis D. Chesley, Jr., M.D.

Centers for Disease Control and Prevention
Wayne Giles, M.D., M.P.H.

Coordinating Committee for the Community Demonstration Studies
Thomas M. Lasater, Ph.D.

Department of Agriculture
Alanna Moshfegh, M.S., R.D.

Department of Defense
Col. Robert Dana Bradshaw, M.D., M.P.H.

Food and Drug Administration
Elizabeth Yetley, Ph.D.

Health Resources and Services Administration
Celia Hayes, M.P.H., R.D.

National Cancer Institute
Carolyn Clifford, Ph.D.

National Center for Health Statistics
Clifford Johnson, M.P.H.

Office of Disease Prevention and Health Promotion
Elizabeth Castro, Ph.D.

Department of Veterans Affairs
Pamela Steele, M.D.

Contents

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III)

Executive Summary

Introduction

The Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III, or ATP III) constitutes the National Cholesterol Education Program's (NCEP's) updated clinical guidelines for cholesterol testing and management. The full ATP III document is an evidence-based and extensively referenced report that provides the scientific rationale for the recommendations contained in the executive summary. ATP III builds on previous ATP reports and expands the indications for intensive cholesterol-lowering therapy in clinical practice. It should be noted that these guidelines are intended to inform, not replace, the physician's clinical judgment, which must ultimately determine the appropriate treatment for each individual.

Background

The third ATP report updates the existing recommendations for clinical management of high blood cholesterol. The NCEP periodically produces ATP clinical updates as warranted by advances in the science of cholesterol management. Each of the guideline reports—ATP I, II, and III—has a major thrust. ATP I outlined a strategy for primary prevention of coronary heart disease (CHD) in persons with high levels of low density lipoprotein (LDL) cholesterol (≥160 mg/dL) or those with borderline-high LDL cholesterol (130-159 mg/dL) and multiple (2+) risk factors. ATP II affirmed the importance of this approach and added a new feature: the intensive management of LDL cholesterol in persons with established CHD. For CHD patients, ATP II set a new, lower LDL cholesterol goal of ≤100 mg/dL. ATP III adds a call for more intensive LDL-lowering therapy in certain groups of people, in accord with recent clinical trial evidence, but its core is based on ATP I and ATP II. Some of the important features shared with previous reports are shown in Table A in the Appendix.

While ATP III maintains attention to intensive treatment of patients with CHD, its major new feature is a focus on primary prevention in persons with multiple risk factors. Many of these persons have a relatively high risk for CHD and will benefit from more intensive LDL-lowering treatment than recommended in ATP II. Table 1 shows the new features of ATP III.

Table 1. New Features of ATP III

Focus on Multiple Risk Factors

- Raises persons with diabetes without CHD, most of whom display multiple risk factors, to the risk level of CHD risk equivalent.
- Uses Framingham projections of 10-year absolute CHD risk (i.e., the percent probability of having a CHD event in 10 years) to identify certain patients with multiple (2+) risk factors for more intensive treatment.
- Identifies persons with multiple metabolic risk factors (metabolic syndrome) as candidates for intensified therapeutic lifestyle changes.

Modifications of Lipid and Lipoprotein Classification

- Identifies LDL cholesterol <100 mg/dL as optimal.
- Raises categorical low HDL cholesterol from <35 mg/dL to <40 mg/dL because the latter is a better measure of a depressed HDL.
- Lowers the triglyceride classification cutpoints to give more attention to moderate elevations.

Support for Implementation

- Recommends a complete lipoprotein profile (total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides) as the preferred initial test, rather than screening for total cholesterol and HDL alone.
- Encourages use of plant stanols/sterols and viscous (soluble) fiber as therapeutic dietary options to enhance lowering of LDL cholesterol.
- Presents strategies for promoting adherence to therapeutic lifestyle changes and drug therapies.
- Recommends treatment beyond LDL lowering for persons with triglycerides ≥200 mg/dL.

LDL Cholesterol: The Primary Target of Therapy

Research from experimental animals, laboratory investigations, epidemiology, and genetic forms of hypercholesterolemia indicate that elevated LDL cholesterol is a major cause of CHD. In addition, recent clinical trials robustly show that LDL-lowering therapy reduces risk for CHD. For these reasons, ATP III continues to identify elevated LDL cholesterol as the primary target of cholesterol-lowering therapy. As a result, the primary goals of therapy and the cutpoints for initiating treatment are stated in terms of LDL.

Risk Assessment: First Step in Risk Management

A basic principle of prevention is that the intensity of risk-reduction therapy should be adjusted to a person's absolute risk. Hence, the first step in selection of LDL-lowering therapy is to assess a person's risk status. Risk assessment requires measurement of LDL cholesterol as part of lipoprotein analysis and identification of accompanying risk determinants.

In all adults aged 20 years or older, a fasting lipoprotein profile (total cholesterol, LDL cholesterol, high density lipoprotein (HDL) cholesterol, and triglyceride) should be obtained once every 5 years. If the testing opportunity is nonfasting, only the values for total cholesterol and HDL cholesterol will be usable. In such a case, if total cholesterol is ≥200 mg/dL or HDL is <40 mg/dL, a followup lipoprotein profile is needed for appropriate management based on LDL. The relationship between LDL cholesterol levels and CHD risk is continuous over a broad range of LDL levels from low to high. Therefore, ATP III adopts the classification of LDL cholesterol levels shown in Table 2, which also shows the classification of total and HDL cholesterol levels.

Table 2. ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)

LDL Cholesterol	
<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-189	High
≥190	Very high
Total Cholesterol	
<200	Desirable
200-239	Borderline high
≥240	High
HDL Cholesterol	
<40	Low
≥60	High

Risk determinants in addition to LDL-cholesterol include the presence or absence of CHD, other clinical forms of atherosclerotic disease, and the major risk factors other than LDL (see Table 3). (LDL is not counted among the risk factors in Table 3 because the purpose of counting those risk factors is to modify the treatment of LDL.) Based on these other risk determinants, ATP III identifies three categories of risk that modify the goals and modalities of LDL-lowering therapy. Table 4 defines these categories and shows corresponding LDL-cholesterol goals.

Table 3. Major Risk Factors (Exclusive of LDL Cholesterol) That Modify LDL Goals*

- Cigarette smoking
- Hypertension (BP ≥140/90 mmHg or on antihypertensive medication)
- Low HDL cholesterol (<40 mg/dL)†
- Family history of premature CHD (CHD in male first degree relative <55 years; CHD in female first degree relative <65 years)
- Age (men ≥45 years; women ≥55 years)*

* *In ATP III, diabetes is regarded as a CHD risk equivalent.*

† *HDL cholesterol ≥60 mg/dL counts as a "negative" risk factor; its presence removes one risk factor from the total count.*

Table 4. Three Categories of Risk that Modify LDL Cholesterol Goals

Risk Category	LDL Goal (mg/dL)
CHD and CHD risk equivalents	<100
Multiple (2+) risk factors*	<130
Zero to one risk factor	<160

** Risk factors that modify the LDL goal are listed in Table 3*

The category of highest risk consists of CHD and CHD risk equivalents. The latter carry a risk for major coronary events equal to that of established CHD, i.e., >20% per 10 years (i.e., more than 20 of 100 such individuals will develop CHD or have a recurrent CHD event within 10 years). CHD risk equivalents comprise:

- Other clinical forms of atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, and symptomatic carotid artery disease);
- Diabetes;
- Multiple risk factors that confer a 10-year risk for CHD >20%.

Diabetes counts as a CHD risk equivalent because it confers a high risk of new CHD within 10 years, in part because of its frequent association with multiple risk factors. Furthermore, because persons with diabetes who experience a myocardial infarction have an unusually high death rate either immediately or in the long term, a more intensive prevention strategy is warranted. Persons with CHD or CHD risk equivalents have the lowest LDL cholesterol goal (<100 mg/dL).

The second category consists of persons with multiple (2+) risk factors in whom 10-year risk for CHD is ≤20%. Risk is estimated from Framingham risk scores (see Appendix). The major risk factors, exclusive of elevated LDL cholesterol, are used to define the presence of multiple risk factors that modify the goals and cutpoints for LDL-lowering treatment, and these are listed in Table 3. The LDL cholesterol goal for persons with multiple (2+) risk factors is <130 mg/dL.

The third category consists of persons having 0-1 risk factor; with few exceptions, persons in this category have a 10-year risk <10%. Their LDL cholesterol goal is <160 mg/dL.

Method of risk assessment: counting major risk factors and estimating 10-year CHD risk

Risk status in persons *without* clinically manifest CHD or other clinical forms of atherosclerotic disease is determined by a 2-step procedure.

First, the number of risk factors is counted (Table 3). Second, for persons with multiple (2+) risk factors, 10-year risk assessment is carried out with Framingham scoring (see Appendix) to identify individuals whose short-term (10-year) risk warrants consideration of intensive treatment. Estimation of the 10-year CHD risk adds a step to risk assessment beyond risk factor counting, but this step is warranted because it allows better targeting of intensive treatment to people who will benefit from it. When 0-1 risk factor is present, Framingham scoring is not necessary because 10-year risk rarely reaches levels for intensive intervention; a very high LDL level in such a person may nevertheless warrant consideration of drug therapy to reduce long-term risk. Risk factors used in Framingham scoring include age, total cholesterol, HDL cholesterol, blood pressure, and cigarette smoking. Total cholesterol is used for 10-year risk assessment because of a larger and more robust Framingham database for total than for LDL cholesterol, but LDL cholesterol is the primary target of therapy. Framingham scoring divides persons with multiple risk factors into those with 10-year risk for CHD of >20%, 10-20%, and <10%. It should be noted that this 2-step sequence can be reversed with essentially the same results.* Initial risk assessment in ATP III uses the major risk factors to define the core risk status. Only after the core risk status has been determined should any other risk modifiers be taken into consideration for adjusting the therapeutic approach.

Role of other risk factors in risk assessment

ATP III recognizes that risk for CHD is influenced by other factors not included among the major, independent risk factors (Table 3). Among these are *life-habit risk factors* and *emerging risk factors.* The former include obesity, physical inactivity, and atherogenic diet; the latter consist of lipoprotein (a), homocysteine, prothrombotic and proinflammatory factors, impaired fasting glucose, and evidence of subclinical atherosclerotic disease. The *life-habit risk factors* are direct targets for clinical intervention, but are not used to set a lower LDL cholesterol goal of therapy. The *emerging risk factors* do not categorically modify LDL cholesterol goals; however, they appear to contribute to CHD risk to varying degrees and can have utility in selected persons to guide intensity of risk-reduction therapy. Their presence can modulate clinical judgment when making therapeutic decisions.

Metabolic syndrome

Many persons have a constellation of major risk factors, life-habit risk factors, and emerging risk factors that constitute a condition called the

*If Framingham scoring is carried out *before* risk factor counting, persons with <10 percent risk are then divided into those with 2+ risk factors and 0-1 risk factor by risk factor counting to determine the appropriate LDL goal (see Table 4).

metabolic syndrome. Factors characteristic of the metabolic syndrome are abdominal obesity, atherogenic dyslipidemia (elevated triglyceride, small LDL particles, low HDL cholesterol), raised blood pressure, insulin resistance (with or without glucose intolerance), and prothrombotic and proinflammatory states. ATP III recognizes the metabolic syndrome as a secondary target of risk-reduction therapy, after the primary target—LDL cholesterol. Diagnosis and treatment of the metabolic syndrome is described beginning on page 15 under "Benefit Beyond LDL Lowering: The Metabolic Syndrome as a Secondary Target of Therapy."

The link between risk assessment and cost effectiveness

In ATP III, a primary aim is to match intensity of LDL-lowering therapy with absolute risk. Everyone with elevated LDL cholesterol is treated with lifestyle changes that are effective in lowering LDL levels. Persons at relatively high risk are also candidates for drug treatment, which is very effective but entails significant additional expense. The cutpoints for drug treatment are based primarily on risk-benefit considerations: those at higher risk are likely to get greater benefit. However, cutpoints for recommended management based on therapeutic efficacy are checked against currently accepted standards for cost effectiveness. Lifestyle changes are the most cost-effective means to reduce risk for CHD. Even so, to achieve maximal benefit, many persons will require LDL-lowering drugs. Drug therapy is the major expense of LDL-lowering therapy, and it dominates cost-effectiveness analysis. However, the costs of LDL-lowering drugs are currently in flux and appear to be declining. This report recognizes that as drug prices decline it will be possible to extend drug use to lower risk persons and still be cost effective. In addition, ATP III recognizes that some persons with high long-term risk are candidates for LDL-lowering drugs even though use of drugs may not be cost effective by current standards.

Primary Prevention With LDL-Lowering Therapy

Primary prevention of CHD offers the greatest opportunity for reducing the burden of CHD in the United States. The clinical approach to primary prevention is founded on the public health approach that calls for lifestyle changes, including: 1) reduced intakes of saturated fat and cholesterol, 2) increased physical activity, and 3) weight control, to lower population cholesterol levels and reduce CHD risk, but the clinical approach intensifies preventive strategies for higher risk persons. One aim of primary prevention is to reduce long-term risk (>10 years) as well as short-term risk (≤10 years). LDL goals in primary prevention depend on a person's absolute risk for CHD (i.e., the probability of having a CHD

event in the short term or the long term)—the higher the risk, the lower the goal. Therapeutic lifestyle changes are the foundation of clinical primary prevention. Nonetheless, some persons at higher risk because of high or very high LDL cholesterol levels or because of multiple risk factors are candidates for LDL-lowering drugs. Recent primary prevention trials show that LDL-lowering drugs reduce risk for major coronary events and coronary death even in the short term.

Any person with elevated LDL cholesterol or other form of hyperlipidemia should undergo clinical or laboratory assessment to rule out secondary dyslipidemia before initiation of lipid-lowering therapy. Causes of secondary dyslipidemia include:

- Diabetes
- Hypothyroidism
- Obstructive liver disease
- Chronic renal failure
- Drugs that increase LDL cholesterol and decrease HDL cholesterol (progestins, anabolic steroids, and corticosteroids).

Once secondary causes have been excluded or, if appropriate, treated, the goals for LDL-lowering therapy in primary prevention are established according to a person's risk category (Table 4).

Secondary Prevention With LDL-Lowering Therapy

Recent clinical trials demonstrate that LDL-lowering therapy reduces total mortality, coronary mortality, major coronary events, coronary artery procedures, and stroke in persons with established CHD. As shown in Table 2, an LDL cholesterol level of <100 mg/dL is *optimal;* therefore, ATP III specifies an LDL cholesterol <100 mg/dL as the goal of therapy in secondary prevention. This goal is supported by clinical trials with both clinical and angiographic endpoints and by prospective epidemiological studies. The same goal should apply for persons with CHD risk equivalents. When persons are hospitalized for acute coronary syndromes or coronary procedures, lipid measures should be taken on admission or within 24 hours. These values can guide the physician on initiation of LDL-lowering therapy before or at discharge. Adjustment of therapy may be needed after 12 weeks.

LDL-Lowering Therapy in Three Risk Categories

The two major modalities of LDL-lowering therapy are *therapeutic lifestyle changes* (TLC) and *drug therapy.* Both are described in more detail later. The TLC Diet stresses reductions in saturated fat and cholesterol intakes. When the metabolic syndrome or its associated lipid risk factors (elevated

triglyceride or low HDL cholesterol) are present, TLC also stresses weight reduction and increased physical activity. Table 5 defines LDL cholesterol goals and cutpoints for initiation of TLC and for drug consideration for persons with three categories of risk: CHD and CHD risk equivalents; multiple (2+) risk factors (10-year risk 10-20% and <10%); and 0-1 risk factor.

Table 5: LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories.

Risk Category	LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)*
2+ Risk Factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20%: ≥130 mg/dL 10-year risk <10%: ≥160 mg/dL
0-1 Risk Factor†	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

* *Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.*

† *Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.*

CHD and CHD risk equivalents

For persons with CHD and CHD risk equivalents, LDL-lowering therapy greatly reduces risk for major coronary events and stroke and yields highly favorable cost-effectiveness ratios. The cut-points for initiating lifestyle and drug therapies are shown in Table 5.

- *If baseline LDL cholesterol is ≥130 mg/dL*, intensive lifestyle therapy and maximal control of other risk factors should be started. Moreover, for most patients, an LDL-lowering drug will be required to achieve an LDL cholesterol <100 mg/dL; thus an LDL cholesterol lowering drug can be started simultaneously with TLC to attain the goal of therapy.

- *If LDL cholesterol levels are 100-129 mg/dL*, either at baseline or on LDL-lowering therapy, several therapeutic approaches are available:

- Initiate or intensify lifestyle and/or drug therapies specifically to lower LDL.
- Emphasize weight reduction and increased physical activity in persons with the metabolic syndrome.
- Delay use or intensification of LDL-lowering therapies and institute treatment of other lipid or nonlipid risk factors; consider use of other lipid-modifying drugs (e.g., nicotinic acid or fibric acid) if the patient has elevated triglyceride or low HDL cholesterol.

- *If baseline LDL cholesterol is <100 mg/dL*, further LDL-lowering therapy is not required. Patients should nonetheless be advised to follow the TLC Diet on their own to help keep the LDL level optimal. Several clinical trials are currently underway to assess benefit of lowering LDL cholesterol to well below 100 mg/dL. At present, emphasis should be placed on controlling other lipid and nonlipid risk factors and on treatment of the metabolic syndrome, if present.

Multiple (2+) risk factors and 10-year risk ≤20%

For persons with multiple (2+) risk factors and 10-year risk ≤ 20%, intensity of therapy is adjusted according to 10-year risk and LDL cholesterol level. The treatment approach for each category is summarized in Table 5.

- *Multiple (2+) risk factors and a 10-year risk of 10-20%*. In this category, the goal for LDL cholesterol is <130 mg/dL. The therapeutic aim is to reduce short-term risk as well as long-term risk for CHD. If baseline LDL cholesterol is ≥130 mg/dL, TLC is initiated and maintained for 3 months. If LDL remains ≥130 mg/dL after 3 months of TLC, consideration can be given to starting an LDL-lowering drug to achieve the LDL goal of <130 mg/dL. Use of LDL-lowering drugs at this risk level reduces CHD risk and is cost-effective. If the LDL falls to less than 130 mg/dL on TLC alone, TLC can be continued without adding drugs. In older persons (≥65 years), clinical judgment is required for how intensively to apply these guidelines; a variety of factors, including concomitant illnesses, general health status, and social issues may influence treatment decisions and may suggest a more conservative approach.

- *Multiple (2+) risk factors and a 10-year risk of <10%*. In this category, the goal for LDL cholesterol also is <130 mg/dL. The therapeutic aim, however, is primarily to reduce longer-term risk. If baseline LDL cholesterol is ≥130 mg/dL, the TLC Diet is initiated to reduce LDL cholesterol. If LDL is <160 mg/dL on TLC alone, it should be continued. LDL-lowering drugs generally are not recommended because the patient is not at high short-term risk. On the other hand, if

LDL cholesterol is ≥160 mg/dL, drug therapy can be considered to achieve an LDL cholesterol <130 mg/dL; the primary aim is to reduce long-term risk. Cost-effectiveness is marginal, but drug therapy can be justified to slow development of coronary atherosclerosis and to reduce long-term risk for CHD.

Zero to one risk factor

Most persons with 0-1 risk factor have a 10-year risk <10%. They are managed according to Table 5. The goal for LDL cholesterol in this risk category is <160 mg/dL. The primary aim of therapy is to reduce long-term risk. First-line therapy is TLC. If after 3 months of TLC the LDL cholesterol is <160 mg/dL, TLC is continued. However, if LDL cholesterol is 160-189 mg/dL after an adequate trial of TLC, drug therapy is *optional* depending on clinical judgment. Factors favoring use of drugs include:

- A severe single risk factor (heavy cigarette smoking, poorly controlled hypertension, strong family history of premature CHD, or very low HDL cholesterol);
- Multiple life-habit risk factors and emerging risk factors (if measured);
- 10-year risk approaching 10% (if measured; see Appendix).

If LDL cholesterol is ≥190 mg/dL despite TLC, drug therapy should be considered to achieve the LDL goal of <160 mg/dL.

The purpose of using LDL-lowering drugs in persons with 0-1 risk factor and elevated LDL cholesterol (≥160 mg/dL) is to slow the development of coronary atherosclerosis, which will reduce long-term risk. This aim may conflict with cost-effectiveness considerations; thus, clinical judgment is required in selection of persons for drug therapy, although a strong case can be made for using drugs when LDL cholesterol is ≥190 mg/dL after TLC.

For persons whose LDL cholesterol levels are already below goal levels upon first encounter, instructions for appropriate changes in life habits, periodic followup, and control of other risk factors are needed.

Therapeutic Lifestyle Changes in LDL-Lowering Therapy

ATP III recommends a multifaceted lifestyle approach to reduce risk for CHD. This approach is designated *therapeutic lifestyle changes (TLC).* Its essential features are:

- Reduced intakes of saturated fats (<7% of total calories) and cholesterol (<200 mg per day) (see Table 6 for overall composition of the TLC Diet)
- Therapeutic options for enhancing LDL lowering such as plant stanols/sterols (2 g/day) and increased viscous (soluble) fiber (10-25 g/day)
- Weight reduction
- Increased physical activity

Table 6. Nutrient Composition of the TLC Diet

Nutrient	Recommended Intake
Saturated fat*	Less than 7% of total calories
Polyunsaturated fat	Up to 10% of total calories
Monounsaturated fat	Up to 20% of total calories
Total fat	25-35% of total calories
Carbohydrate†	50-60% of total calories
Fiber	20-30 g/day
Protein	Approximately 15% of total calories
Cholesterol	Less than 200 mg/day
Total calories (energy)‡	Balance energy intake and expenditure to maintain desirable body weight/prevent weight gain

** Trans fatty acids are another LDL-raising fat that should be kept at a low intake.*
† Carbohydrate should be derived predominantly from foods rich in complex carbohydrates including grains, especially whole grains, fruits, and vegetables.
‡ Daily energy expenditure should include at least moderate physical activity (contributing approximately 200 Kcal per day).

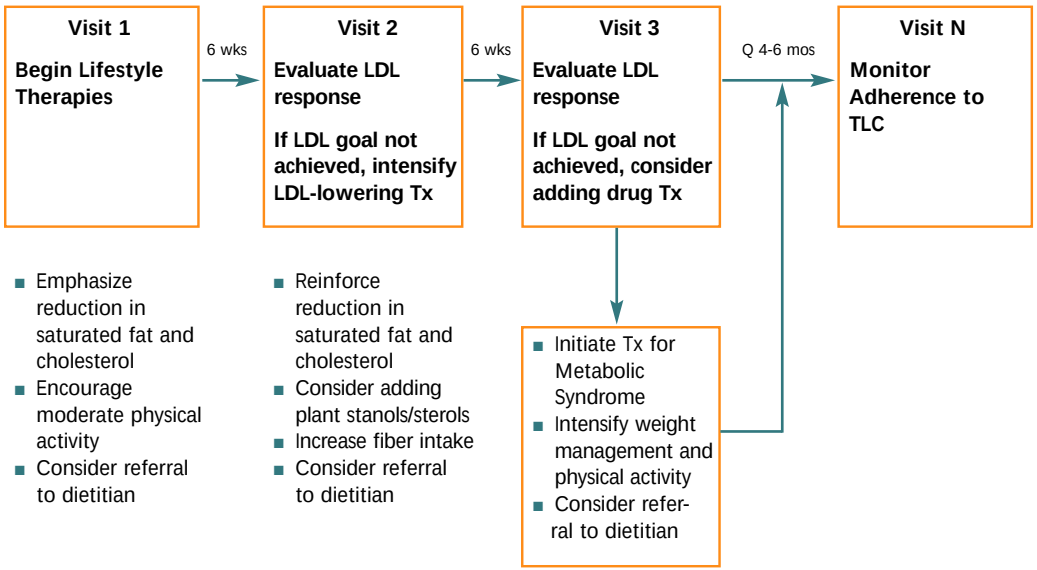
A model of steps in TLC is shown in Figure 1. To initiate TLC, intakes of saturated fats and cholesterol are reduced first to lower LDL cholesterol. To improve overall health, ATP III's TLC Diet generally contains the recommendations embodied in the Dietary Guidelines for Americans 2000. One exception is that total fat is allowed to range from 25-35% of total calories provided saturated fats and *trans* fatty acids are kept low. A higher intake of total fat, mostly in the form of unsaturated fat, can help to reduce triglycerides and raise HDL cholesterol in persons with the metabolic syndrome. In accordance with the Dietary Guidelines, moderate physical activity is encouraged. After 6 weeks, the LDL response is determined; if the LDL cholesterol goal has not been achieved, other therapeutic options for LDL lowering such as plant stanol/sterols and viscous fiber can be added.

After maximum reduction of LDL cholesterol with dietary therapy, emphasis shifts to management of the metabolic syndrome and associated lipid risk factors. The majority of persons with these latter abnormalities are overweight or obese and sedentary. Weight reduction therapy for overweight or obese patients will enhance LDL lowering and will provide other health benefits including modifying other lipid and nonlipid risk factors.

Assistance in the management of overweight and obese persons is provided by the *Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults* from the NHLBI Obesity Education Initiative (1998). Additional risk reduction can be achieved by simultaneously increasing physical activity.

At all stages of dietary therapy, physicians are encouraged to refer patients to registered dietitians or other qualified nutritionists for *medical nutrition therapy,* which is the term for the nutritional intervention and guidance provided by a nutrition professional.

Figure 1. A Model of Steps in Therapeutic Lifestyle Changes (TLC)



Drug Therapy to Achieve LDL Cholesterol Goals

A portion of the population whose short-term or long-term risk for CHD is high will require LDL-lowering drugs in addition to TLC to reach the designated goal for LDL cholesterol (see Table 5). When drugs are prescribed, attention to TLC should always be maintained and reinforced. Currently available drugs that affect lipoprotein metabolism and their major characteristics are listed in Table 7.

Some cholesterol-lowering agents are currently available over-the-counter (OTC) (e.g., nicotinic acid), and manufacturers of several classes of LDL-lowering drugs (e.g., statins, bile acid sequestrants) have applied to the

Table 7. Drugs Affecting Lipoprotein Metabolism

Drug Class, Agents and Daily Doses	Lipid/Lipoprotein Effects		Side Effects	Contraindications	Clinical Trial Results
HMG CoA reductase inhibitors (statins)*	LDL HDL TG	↓18-55% ↑5-15% ↓7-30%	Myopathy Increased liver enzymes	Absolute: • Active or chronic liver disease Relative: • Concomitant use of certain drugs†	Reduced major coronary events, CHD deaths, need for coronary procedures, stroke, and total mortality
Bile acid Sequestrants‡	LDL HDL TG	↓15-30% ↑3-5% No change or increase	Gastrointestinal distress Constipation Decreased absorption of other drugs	Absolute: • dysbeta-lipoproteinemia • TG >400 mg/dL Relative: • TG >200 mg/dL	Reduced major coronary events and CHD deaths
Nicotinic acid¥	LDL HDL TG	↓ 5-25% ↑15-35% ↓20-50%	Flushing Hyperglycemia Hyperuricemia (or gout) Upper GI distress Hepatotoxicity	Absolute: • Chronic liver disease • Severe gout Relative: • Diabetes • Hyperuricemia • Peptic ulcer disease	Reduced major coronary events, and possibly total mortality
Fibric acids§	LDL *(may be increased in patients with high TG)* HDL TG	↓5-20% ↑10-20% ↓20-50%	Dyspepsia Gallstones Myopathy Unexplained non-CHD deaths in WHO study	Absolute: • Severe renal disease • Severe hepatic disease	Reduced major coronary events

* *Lovastatin (20-80 mg), pravastatin (20-40 mg), simvastatin (20-80 mg), fluvastatin (20-80 mg), atorvastatin (10-80 mg), cerivastatin (0.4-0.8 mg).*

† *Cyclosporine, macrolide antibiotics, various antifungal agents and cytochrome P-450 inhibitors (fibrates and niacin should be used with appropriate caution).*

‡ *Cholestyramine (4-16 g), colestipol (5-20 g), colesevelam (2.6-3.8 g).*

¥ *Immediate release (crystalline) nicotinic acid (1.5-3 g), extended release nicotinic acid (Niaspan ®) (1-2 g), sustained release nicotinic acid (1-2 g).*

§ *Gemfibrozil (600 mg BID), fenofibrate (200 mg), clofibrate (1000 mg BID).*

Food and Drug Administration (FDA) to allow these agents to become OTC medications. At the time of publication of ATP III, the FDA has not granted permission for OTC status for statins or bile acid sequestrants. If an OTC cholesterol-lowering drug is or becomes available, patients should continue to consult with their physicians about whether to initiate drug treatment, about setting the goals of therapy, and about monitoring for therapeutic responses and side effects.

Secondary prevention: drug therapy for CHD and CHD risk equivalents

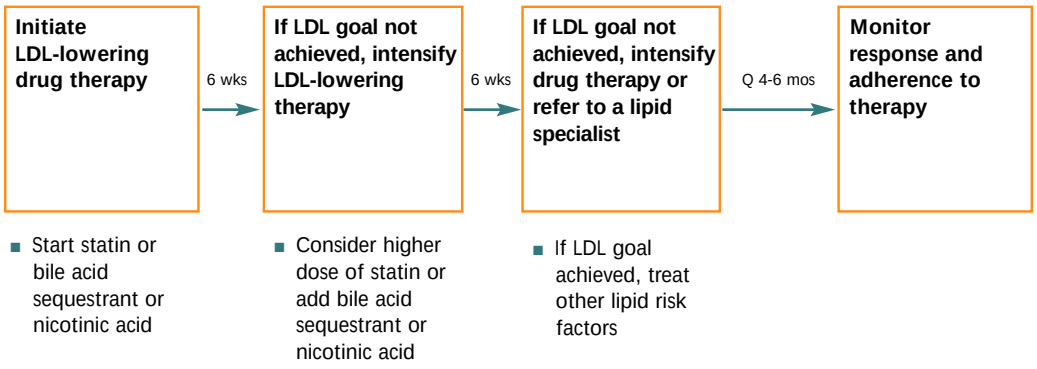
For persons with CHD and CHD risk equivalents, the goal is to attain an LDL cholesterol level <100 mg/dL. The cutpoints for initiating lifestyle and drug therapies are shown in Table 5, and the approach to treatment is discussed immediately after Table 5. Most CHD patients will need LDL-lowering drug therapy. Other lipid risk factors may also warrant consideration of drug treatment. Whether or not lipid-modifying drugs are used, nonlipid risk factors require attention and favorable modification.

In persons admitted to the hospital for a major coronary event, LDL cholesterol should be measured on admission or within 24 hours. This value can be used for treatment decisions. In general, persons hospitalized for a coronary event or procedure should be discharged on drug therapy if the LDL cholesterol is ≥130 mg/dL. If the LDL is 100–129 mg/dL, clinical judgment should be used in deciding whether to initiate drug treatment at discharge, recognizing that LDL cholesterol levels begin to decline in the first few hours after an event and are significantly decreased by 24-48 hours and may remain low for many weeks. Thus, the initial LDL cholesterol level obtained in the hospital may be substantially lower than is usual for the patient. Some authorities hold drug therapy should be initiated whenever a patient hospitalized for a CHD-related illness is found to have an LDL cholesterol >100 mg/dL. Initiation of drug therapy at the time of hospital discharge has two advantages. First, at that time patients are particularly motivated to undertake and adhere to risk-lowering interventions; and second, failure to initiate indicated therapy early is one of the causes of a large "treatment gap," because outpatient followup is often less consistent and more fragmented.

LDL-lowering drug therapy for primary prevention

Table 5 shows the cutpoints for considering drug treatment in primary prevention. The general approach to management of drug therapy for primary prevention is outlined in Figure 2.

Figure 2. Progression of Drug Therapy in Primary Prevention



When drug therapy for primary prevention is a consideration, the third visit of dietary therapy (see Figure 1) will typically be the visit to initiate drug treatment. Even if drug treatment is started, TLC should be continued. As with TLC, the first priority of drug therapy is to achieve the goal for LDL cholesterol. For this reason, an LDL-lowering drug should be started. The usual drug will be a statin, but alternatives are a bile acid sequestrant or nicotinic acid. In most cases, the statin should be started at a moderate dose. In many patients, the LDL cholesterol goal will be achieved, and higher doses will not be necessary. The patient's response should be checked about 6 weeks after starting drug therapy. If the goal of therapy has been achieved, the current dose can be maintained. However, if the goal has not been achieved, LDL-lowering therapy can be intensified, either by increasing the dose of statin or by combining a statin with a bile acid sequestrant or nicotinic acid.

After 12 weeks of drug therapy, the response to therapy should again be assessed. If the LDL cholesterol goal is still not achieved, consideration can be given to further intensification of drug therapy. If the LDL goal cannot be attained by standard lipid-lowering therapy, consideration should be given to seeking consultation from a lipid specialist. Once the goal for LDL cholesterol has been attained, attention can turn to other lipid risk factors and nonlipid factors. Thereafter, patients can be monitored for response to therapy every 4 to 6 months, or more often if considered necessary.

Benefit Beyond LDL Lowering: The Metabolic Syndrome as a Secondary Target of Therapy

Evidence is accumulating that risk for CHD can be reduced beyond LDL-lowering therapy by modification of other risk factors. One potential

secondary target of therapy is the metabolic syndrome, which represents a constellation of lipid and nonlipid risk factors of metabolic origin. This syndrome is closely linked to a generalized metabolic disorder called *insulin resistance* in which the normal actions of insulin are impaired. Excess body fat (particularly abdominal obesity) and physical inactivity promote the development of insulin resistance, but some individuals also are genetically predisposed to insulin resistance.

The risk factors of the metabolic syndrome are highly concordant; in aggregate they enhance risk for CHD at any given LDL cholesterol level. For purposes of ATP III, the diagnosis of the metabolic syndrome is made when three or more of the risk determinants shown in Table 8 are present. These determinants include a combination of categorical and borderline risk factors that can be readily measured in clinical practice.

Table 8. Clinical Identification of the Metabolic Syndrome

Risk Factor	Defining Level
Abdominal Obesity*	Waist Circumference†
Men	>102 cm (>40 in)
Women	>88 cm (>35 in)
Triglycerides	≥150 mg/dL
HDL cholesterol	
Men	<40 mg/dL
Women	<50 mg/dL
Blood pressure	≥130/≥85 mmHg
Fasting glucose	≥110 mg/dL

* *Overweight and obesity are associated with insulin resistance and the metabolic syndrome. However, the presence of abdominal obesity is more highly correlated with the metabolic risk factors than is an elevated body mass index (BMI). Therefore, the simple measure of waist circumference is recommended to identify the body weight component of the metabolic syndrome.*

† *Some male patients can develop multiple metabolic risk factors when the waist circumference is only marginally increased, e.g., 94-102 cm (37-39 in). Such patients may have a strong genetic contribution to insulin resistance. They should benefit from changes in life habits, similarly to men with categorical increases in waist circumference.*

Management of the metabolic syndrome has a two-fold objective: (1) to reduce underlying causes (i.e., obesity and physical inactivity), and (2) to treat associated nonlipid and lipid risk factors.

Management of underlying causes of the metabolic syndrome

First-line therapies for all lipid and nonlipid risk factors associated with the metabolic syndrome are weight reduction and increased physical activity, which will effectively reduce all of these risk factors. Therefore, after

appropriate control of LDL cholesterol, TLC should stress weight reduction and physical activity if the metabolic syndrome is present.

Weight control. In ATP III overweight and obesity are recognized as major, underlying risk factors for CHD and identified as direct targets of intervention. Weight reduction will enhance LDL lowering and reduce all of the risk factors of the metabolic syndrome. The recommended approaches for reducing overweight and obesity are contained in the clinical guidelines of the NHLBI Obesity Education Initiative.

Physical activity. Physical inactivity is likewise a major, underlying risk factor for CHD. It augments the lipid and nonlipid risk factors of the metabolic syndrome. It further may enhance risk by impairing cardiovascular fitness and coronary blood flow. Regular physical activity reduces very low density lipoprotein (VLDL) levels, raises HDL cholesterol, and in some persons, lowers LDL levels. It also can lower blood pressure, reduce insulin resistance, and favorably influence cardiovascular function. Thus, ATP III recommends that regular physical activity become a routine component in management of high serum cholesterol. The evidence base for this recommendation is contained in the *U.S. Surgeon General's Report on Physical Activity.*

Specific Treatment of Lipid and Non-Lipid Risk Factors

Beyond the underlying risk factors, therapies directed against the lipid and nonlipid risk factors of the metabolic syndrome will reduce CHD risk. These include treatment of hypertension, use of aspirin in patients with CHD to reduce the prothrombotic state (guidelines for aspirin use in primary prevention have not been firmly established), and treatment of elevated triglycerides and low HDL cholesterol as discussed below under Management of Specific Dyslipidemias.

Special Issues

Management of Specific Dyslipidemias

Very high LDL cholesterol (≥190 mg/dL). Persons with very high LDL cholesterol usually have genetic forms of hypercholesterolemia: monogenic familial hypercholesterolemia, familial defective apolipoprotein B, and polygenic hypercholesterolemia. Early detection of these disorders through cholesterol testing in young adults is needed to prevent premature CHD. Family testing is important to identify similarly affected relatives. These

disorders often require combined drug therapy (statin + bile acid sequestrant) to achieve the goals of LDL-lowering therapy.

Elevated serum triglycerides. Recent meta-analyses of prospective studies indicate that elevated triglycerides are also an independent risk factor for CHD. Factors contributing to elevated (higher than normal) triglycerides in the general population include: obesity and overweight, physical inactivity, cigarette smoking, excess alcohol intake, high carbohydrate diets (>60% of energy intake), several diseases (e.g., type 2 diabetes, chronic renal failure, nephrotic syndrome), certain drugs (e.g., corticosteroids, estrogens, retinoids, higher doses of beta-adrenergic blocking agents), and genetic disorders (familial combined hyperlipidemia, familial hypertriglyceridemia, and familial dysbetalipoproteinemia).

In clinical practice, elevated serum triglycerides are most often observed in persons with the metabolic syndrome, although secondary or genetic factors can heighten triglyceride levels. ATP III adopts the following classification of serum triglycerides:

- Normal triglycerides: <150 mg/dL
- Borderline-high triglycerides: 150-199 mg/dL
- High triglycerides: 200-499 mg/dL
- Very high triglycerides: ≥500 mg/dL

The finding that elevated triglycerides are an independent CHD risk factor suggests that some triglyceride-rich lipoproteins are atherogenic. The latter are partially degraded VLDL, commonly called *remnant lipoproteins.* In clinical practice, VLDL cholesterol is the most readily available measure of atherogenic remnant lipoproteins. Thus, VLDL cholesterol can be a target of cholesterol-lowering therapy. ATP III identifies the sum of LDL+VLDL cholesterol [termed *non-HDL cholesterol* (total cholesterol minus HDL cholesterol)] as a secondary target of therapy in persons with high triglycerides (≥200 mg/dL). The goal for non-HDL cholesterol in persons with high serum triglycerides can be set at 30 mg/dL higher than that for LDL cholesterol (Table 9) on the premise that a VLDL cholesterol level ≤30 mg/dL is normal.

The treatment strategy for elevated triglycerides depends on the causes of the elevation and its severity. For all persons with elevated triglycerides, the primary aim of therapy is to achieve the target goal for LDL cholesterol. When triglycerides are *borderline high* (150-199 mg/dL), emphasis should also be placed on weight reduction and increased physical activity. For *high triglycerides* (200-499 mg/dL), non-HDL cholesterol becomes a secondary

Table 9. Comparison of LDL Cholesterol and Non-HDL Cholesterol Goals for Three Risk Categories

Risk Category	LDL Goal (mg/dL)	Non-HDL-C Goal (mg/dL)
CHD and CHD Risk Equivalent (10-year risk for CHD >20%)	<100	<130
Multiple (2+) Risk Factors and 10-year risk ≤20%	<130	<160
0-1 Risk Factor	<160	<190

target of therapy. Aside from weight reduction and increased physical activity, drug therapy can be considered in high-risk persons to achieve the non-HDL cholesterol goal. There are two approaches to drug therapy. First, the non-HDL cholesterol goal can be achieved by intensifying therapy with an LDL-lowering drug; or second, nicotinic acid or fibrate can be added, if used with appropriate caution, to achieve the non-HDL cholesterol goal by further lowering of VLDL cholesterol. In rare cases in which triglycerides are *very high* (≥500 mg/dL), the initial aim of therapy is to prevent acute pancreatitis through triglyceride lowering. This approach requires very low fat diets (≤15% of calorie intake), weight reduction, increased physical activity, and usually a triglyceride-lowering drug (fibrate or nicotinic acid). Only after triglyceride levels have been lowered to <500 mg/dL should attention turn to LDL lowering to reduce risk for CHD.

Low HDL cholesterol. Low HDL cholesterol is a strong independent predictor of CHD. In ATP III, low HDL cholesterol is defined categorically as a level <40 mg/dL, a change from the level of <35 mg/dL in ATP II. In the present guidelines, low HDL cholesterol both modifies the goal for LDL-lowering therapy and is used as a risk factor to estimate 10-year risk for CHD.

Low HDL cholesterol levels have several causes, many of which are associated with insulin resistance, i.e., elevated triglycerides, overweight and obesity, physical inactivity, and type 2 diabetes. Other causes are cigarette smoking, very high carbohydrate intakes (>60% of calories), and certain drugs (e.g., beta-blockers, anabolic steroids, progestational agents)

ATP III does not specify a goal for HDL raising. Although clinical trial results suggest that raising HDL will reduce risk, the evidence is insufficient to specify a goal of therapy. Furthermore, currently available drugs do not robustly raise HDL cholesterol. Nonetheless, a low HDL should receive clinical attention and management according to the following sequence. In all persons with low HDL cholesterol, the primary target of therapy is LDL

cholesterol; ATP III guidelines should be followed to achieve the LDL cholesterol goal. Second, after the LDL goal has been reached, emphasis shifts to weight reduction and increased physical activity (when the metabolic syndrome is present). When a low HDL cholesterol is associated with high triglycerides (200-499 mg/dL), secondary priority goes to achieving the non-HDL cholesterol goal, as outlined before. Also, if triglycerides are <200 mg/dL (isolated low HDL cholesterol), drugs for HDL raising (fibrates or nicotinic acid) can be considered; however, treatment for isolated low HDL is mostly reserved for persons with CHD and CHD risk equivalents.

Diabetic dyslipidemia. This disorder is essentially atherogenic dyslipidemia (high triglycerides, low HDL, and small dense LDL) in persons with type 2 diabetes. Although elevated triglycerides and/or low HDL cholesterol are common in persons with diabetes, clinical trial results support the identification of LDL cholesterol as the primary target of therapy, as it is in those without diabetes. Since diabetes is designated a CHD risk equivalent in ATP III, the LDL cholesterol goal of therapy for most persons with diabetes will be <100 mg/dL. Furthermore, when LDL cholesterol is ≥130 mg/dL, most persons with diabetes will require initiation of LDL-lowering drugs simultaneously with TLC to achieve the LDL goal. When LDL cholesterol levels are in the range of 100-129 mg/dL at baseline or on treatment, several therapeutic options are available: increasing intensity of LDL-lowering therapy, adding a drug to modify atherogenic dyslipidemia (fibrate or nicotinic acid), or intensifying control of other risk factors including hyperglycemia. When triglyceride levels are ≥200 mg/dL, non-HDL cholesterol becomes a secondary target of cholesterol-lowering therapy. Several ongoing clinical trials (e.g., Antihypertensive and Lipid Lowering Heart Attack Trial [ALLHAT]) will better quantify the magnitude of the benefit of LDL-lowering treatment in older individuals with diabetes. In older persons (≥65 years of age) with diabetes but no additional CHD risk factors other than age, clinical judgment is required for how intensively to apply these guidelines; a variety of factors, including concomitant illnesses, general health status, and social issues may influence treatment decisions and may suggest a more conservative approach.

Special Considerations for Different Population Groups

Middle-aged men (35-65 years). In general, men have a higher risk for CHD than do women. Middle-aged men in particular have a high prevalence of the major risk factors and are predisposed to abdominal obesity and the metabolic syndrome. A sizable fraction of all CHD in men occurs in middle age. Thus, many middle-aged men carry a relatively high risk for CHD, and for those who do, intensive LDL-lowering therapy is needed.

Women (ages 45-75 years). In women, onset of CHD generally is delayed by some 10-15 years compared with that in men; thus most CHD in women occurs after age 65. All risk factors contribute to CHD in women, and most premature CHD in women (<65 years) occurs in those with multiple risk factors and the metabolic syndrome. Despite the previous belief that the gender difference in risk for CHD reflects a protective effect of estrogen in women, recent secondary and primary prevention trials cast doubt on the use of hormone replacement therapy to reduce CHD risk in postmenopausal women. In contrast, the favorable effects of statin therapy in women in clinical trials make a cholesterol-lowering drug preferable to hormone replacement therapy for CHD risk reduction. Women should be treated similarly to men for secondary prevention. For primary prevention, ATP III's general approach is similarly applicable for women and men. However, the later onset of CHD for women in general should be factored into clinical decisions about use of cholesterol-lowering drugs.

Older adults (men ≥ 65 years and women ≥ 75 years). Overall, most new CHD events and most coronary deaths occur in older persons (≥ 65 years). A high level of LDL cholesterol and low HDL cholesterol still carry predictive power for the development of CHD in older persons. Nevertheless, the finding of advanced subclinical atherosclerosis by noninvasive testing can be helpful for confirming the presence of high risk in older persons. Secondary prevention trials with statins have included a sizable number of older persons, mostly in the age range of 65 to 75 years. In these trials, older persons showed significant risk reduction with statin therapy. Thus, no hard-and-fast age restrictions appear necessary when selecting persons with established CHD for LDL-lowering therapy. For primary prevention, TLC is the first line of therapy for older persons. However, LDL-lowering drugs can also be considered when older persons are at higher risk because of multiple risk factors or advanced subclinical atherosclerosis.

Younger adults (men 20-35 years; women 20-45 years). CHD is rare except in those with severe risk factors, e.g., familial hypercholesterolemia, heavy cigarette smoking, or diabetes. Even though clinical CHD is relatively rare in young adults, coronary atherosclerosis in its early stages may progress rapidly. The rate of development of coronary atherosclerosis earlier in life correlates with the major risk factors. In particular, long-term prospective studies reveal that elevated serum cholesterol detected in young adulthood predicts a higher rate of premature CHD in middle age. Thus, risk factor identification in young adults is an important aim for long-term prevention. The combination of early detection and early intervention on elevated LDL cholesterol with life-habit changes offers the opportunity for delaying or preventing onset of CHD later in life. For young adults with LDL cholesterol levels ≥130 mg/dL, TLC should be instituted and emphasized.

Particular attention should be given to young men who smoke and have a high LDL cholesterol (160-189 mg/dL); they may be candidates for LDL-lowering drugs. When young adults have very high LDL cholesterol levels (≥190 mg/dL), drug therapy should be considered, as in other adults. Those with severe genetic forms of hypercholesterolemia may require LDL-lowering drugs in combination (e.g., statin + bile acid sequestrant).

Racial and ethnic groups. African Americans have the highest overall CHD mortality rate and the highest out-of-hospital coronary death rates of any ethnic group in the United States, particularly at younger ages. Although the reasons for the excess CHD mortality among African Americans have not been fully elucidated, it can be accounted for, at least in part, by the high prevalence of coronary risk factors. Hypertension, left ventricular hypertrophy, diabetes mellitus, cigarette smoking, obesity, physical inactivity, and multiple CHD risk factors all occur more frequently in African Americans than in whites. Other ethnic groups and minority populations in the United States include Hispanics, Native Americans, Asian and Pacific Islanders, and South Asians. Although limited data suggest that racial and ethnic groups vary somewhat in baseline risk for CHD, this evidence did not appear sufficient to lead the ATP III panel to modify general recommendations for cholesterol management in these populations.

Adherence to LDL-Lowering Therapy

Adherence to the ATP III guidelines by both patients and providers is a key to approximating the magnitude of the benefits demonstrated in clinical trials of cholesterol lowering. Adherence issues have to be addressed in order to attain the highest possible levels of CHD risk reduction. Thus, ATP III recommends the use of state-of-the-art multidisciplinary methods targeting the patient, providers, and health delivery systems to achieve the full population effectiveness of the guidelines for primary and secondary prevention (Table 10).

Table 10. Interventions to Improve Adherence

Focus on the Patient

- Simplify medication regimens
- Provide explicit patient instruction and use good counseling techniques to teach the patient how to follow the prescribed treatment
- Encourage the use of prompts to help patients remember treatment regimens
- Use systems to reinforce adherence and maintain contact with the patient
- Encourage the support of family and friends
- Reinforce and reward adherence
- Increase visits for patients unable to achieve treatment goal
- Increase the convenience and access to care
- Involve patients in their care through self-monitoring

Focus on the Physician and Medical Office

- Teach physicians to implement lipid treatment guidelines
- Use reminders to prompt physicians to attend to lipid management
- Identify a patient advocate in the office to help deliver or prompt care
- Use patients to prompt preventive care
- Develop a standardized treatment plan to structure care
- Use feedback from past performance to foster change in future care
- Remind patients of appointments and follow-up missed appointments

Focus on the Health Delivery System

- Provide lipid management through a lipid clinic
- Utilize case management by nurses
- Deploy telemedicine
- Utilize the collaborative care of pharmacists
- Execute critical care pathways in hospitals

Appendix

Shared Features of ATP III and ATP II

ATP III shares a set of core features with ATP II. These are shown in Table A.

Table A. Shared Features of ATP III and ATP II

- Continued identification of LDL cholesterol lowering as the primary goal of therapy
- Consideration of high LDL cholesterol (≥160 mg/dL) as a potential target for LDL-lowering drug therapy, specifically as follows:
  - For persons with multiple risk factors whose LDL levels are high (≥160 mg/dL) after dietary therapy, consideration of drug therapy is recommended
  - For persons with 0-1 risk factor, consideration of drug therapy (after dietary therapy) is optional for LDL 160-189 mg/dL and recommended for LDL ≥190 mg/dL
- Emphasis on intensive LDL-lowering therapy in persons with established CHD
- Identification of three categories of risk for different LDL goals and different intensities of LDL-lowering therapy:
  - CHD and CHD risk equivalents* (other forms of clinical atherosclerotic disease)
  - Multiple (2+) risk factors†
  - 0-1 risk factor
- Identification of subpopulations, besides middle-aged men, for detection of high LDL cholesterol (and other lipid risk factors) and for clinical intervention. These include:
  - Young adults
  - Postmenopausal women
  - Older persons
- Emphasis on weight loss and physical activity to enhance risk reduction in persons with elevated LDL cholesterol

* *A CHD risk equivalent is a condition that carries an absolute risk for developing new CHD equal to the risk for having recurrent CHD events in persons with established CHD.*

† *Risk factors that continue to modify the LDL goal include cigarette smoking, hypertension, low HDL cholesterol, family history of premature CHD, age (male ≥45 years and female ≥55 years), and diabetes (in ATP III diabetes is regarded as a CHD risk equivalent).*

Estimating 10-Year Risk for Men and Women

Risk assessment for determining the 10-year risk for developing CHD is carried out using Framingham risk scoring (Table B1 for men and Table B2 for women). The risk factors included in the Framingham calculation of 10-year risk are: age, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for hypertension, and cigarette smoking. The first step is to calculate the number of points for each risk factor. For initial assessment, values for total cholesterol and HDL cholesterol are required. Because of a larger database, Framingham estimates are more robust for total cholesterol than for LDL cholesterol. Note, however, that the LDL cholesterol level remains the primary target of therapy. Total cholesterol and HDL cholesterol values should be the average of at least two measurements obtained from lipoprotein analysis. The blood pressure value used is that obtained at the time of assessment, regardless of whether the person is on anti-hypertensive therapy. However, if the person is on antihypertensive treatment, an extra point is added beyond points for the blood pressure reading because treated hypertension carries residual risk (see Tables B1 and B2). The average of several blood pressure measurements, as recommended by the Joint National Committee (JNC), is needed for an accurate measure of baseline blood pressure. The designation “smoker” means any cigarette smoking in the past month. The total risk score sums the points for each risk factor. The 10-year risk for myocardial infarction and coronary death (hard CHD) is estimated from total points, and the person is categorized according to absolute 10-year risk as indicated above (see Table 5).

Table B1. Estimate of 10-Year Risk for Men (Framingham Point Scores)

Age	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

	Points				
Total Cholesterol	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Point Total	10-Year Risk %
<0	< 1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
≥17	≥ 30

Table B2. Estimate of 10-Year Risk for Women (Framingham Point Scores)

Age	Points
20-34	-7
35-39	-3
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	12
70-74	14
75-79	16

Total Cholesterol	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	1
200-239	8	6	4	2	1
240-279	11	8	5	3	2
≥280	13	10	7	4	2

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	9	7	4	2	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	1	3
130-139	2	4
140-159	3	5
≥160	4	6

Point Total	10-Year Risk %
<9	< 1
9	1
10	1
11	1
12	1
13	2
14	2
15	3
16	4
17	5
18	6
19	8
20	11
21	14
22	17
23	22
24	27
≥25	≥ 30

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
National Institutes of Health
National Heart, Lung, and Blood Institute

NIH Publication No. 01-3670
May 2001

PDR®

56 EDITION

2002

www.PDR.net

PHYSICIANS' DESK REFERENCE®

PDR® 56 EDITION 2002

PHYSICIANS' DESK REFERENCE®

Executive Vice President, Directory Services: Paul Walsh

Vice President, Sales and Marketing: Dikran N. Barsamian
National Sales Manager: John A. Schmidt
National Sales Manager, Custom Sales: Anthony Sorce
Senior Account Managers: Marion Gray, RPh; Frank Karkowsky
Account Managers: Lawrence C. Keary; Eileen Sullivan; Suzanne E. Yarrow, RN
Director of Trade Sales: Bill Gaffney
Associate Product Manager: Jason R. Springer
Director of Financial Planning and Analysis: Mark S. Ritchin
Vice President, Clinical Communications and New Business Development: Mukesh Mehta, RPh
New Business Development Manager: Jeffrey D. Dubin
Manager, Professional Data Services: Thomas Fleming, PharmD
Manager, Concise Data Content: Christine Wyble, PharmD
Drug Information Specialists: Maria Deutsch, MS, PharmD, CDE; Anu Gupta, PharmD
Editor, Directory Services: David W. Sifton
Project Manager: Edward P. Connor

Senior Associate Editor: Lori Murray
Assistant Editor: Gwynned L. Kelly
Director of Direct Marketing: Michael Bennett
Direct Mail Managers: Jennifer M. Fronzaglia, Lorraine M. Loening
Senior Marketing Analyst: Dina A. Maeder
Promotion Manager: Linda Levine
Director of Production: Brian Holland
Senior Data Manager: Jeffrey D. Schaefer
Production Manager: Amy Brooks
Production Coordinators: Gianna Caradonna, DeeAnn DeRuvo, Melissa Johnson, Christina Klinger
Index Editors: Noel Deloughery, Shannon Reilly
Format Editor: Stu W. Lehrer
Art Associate: Joan K. Akerlind
Digital Imaging Supervisor: Shawn W. Cahill
Digital Imaging Coordinator: Frank J. McElroy, III
Electronic Publishing Designers: Rosalia Sberna, Livio Udina
Fulfillment Managers: Louis J. Bolcik, Stephanie Struble

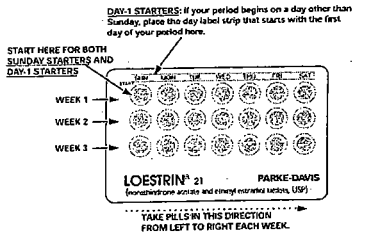
MEDICAL ECONOMICS
THOMSON HEALTHCARE

Officers of Thomson Healthcare: *Chief Executive Officer:* Michael Tansey; *Chief Operating Officer:* Richard Noble; *Chief Financial Officer and Executive Vice President, Finance:* Paul Hilger; *Executive Vice President, Directory Services:* Paul Walsh; *Senior Vice President, Planning and Business Development:* William Gole; *Vice President, Human Resources:* Pamela M. Bilash

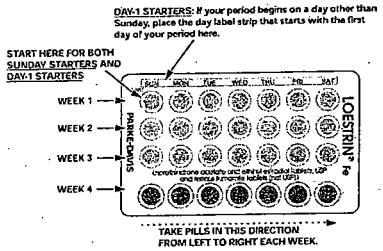
ISBN: 1-56363-411-2

Loestrin—Cont.

3) the week numbers as shown in the following pictures:



Loestrin 21 1/20 will contain: ALL WHITE PILLS
Loestrin 21 1.5/30 will contain: ALL GREEN PILLS



Loestrin Fe 1/20 will contain: 21 WHITE PILLS for WEEKS 1, 2, and 3. WEEK 4 will contain BROWN PILLS ONLY.
Loestrin Fe 1.5/30 will contain: 21 GREEN PILLS for WEEKS 1, 2, and 3. WEEK 4 will contain BROWN PILLS ONLY.
4. BE SURE YOU HAVE READY AT ALL TIMES:
ANOTHER KIND OF BIRTH CONTROL (such as condoms or foam) to use as a back-up in case you miss pills.
An EXTRA, FULL PILL PACK.

WHEN TO START THE FIRST PACK OF PILLS

You have a choice of which day to start taking your first pack of pills. Decide with your doctor or clinic which is the best day for you. Pick a time of day which will be easy to remember.

DAY-1 START:
1. Pick the day label strip that starts with the first day of your period. (This is the day you start bleeding or spotting, even if it is almost midnight when the bleeding begins.).
2. Place this day label strip on the tablet dispenser over the area that has the days of the week (starting with Sunday) printed on the plastic.
3. Take the first "active" white or green pill of the first pack during the first 24 hours of your period.
4. You will not need to use a back-up method of birth control, since you are starting the pill at the beginning of your period.

SUNDAY START:
1. Take the first "active" white or green pill of the first pack on the Sunday after your period starts, even if you are still bleeding. If your period begins on Sunday, start the pack that same day.
2. Use another method of birth control as a back-up method if you have sex anytime from the Sunday you start your first pack until the next Sunday (7 days). Condoms or foam are good back-up methods of birth control.

WHAT TO DO DURING THE MONTH

1. TAKE ONE PILL AT THE SAME TIME EVERY DAY UNTIL THE PACK IS EMPTY.
Do not skip pills even if you are spotting or bleeding between monthly periods or feel sick to your stomach (nausea).
Do not skip pills even if you do not have sex very often.

2. WHEN YOU FINISH A PACK OR SWITCH YOUR BRAND OF PILLS:
21 pills: Wait 7 days to start the next pack. You will probably have your period during that week. Be sure that no more than 7 days pass between 21-day packs.
28 pills: Start the next pack on the day after your last "reminder" pill. Do not wait any days between packs.

WHAT TO DO IF YOU MISS PILLS

If you **MISS 1** white or green "active" pill:
1. Take it as soon as you remember. Take the next pill at your regular time. This means you may take 2 pills in 1 day.
2. You do not need to use a back-up birth control method if you have sex.

If you **MISS 2** white or green "active" pills in a row in **WEEK 1 OR WEEK 2** of your pack:
1. Take 2 pills on the day you remember and 2 pills the next day.
2. Then take 1 pill a day until you finish the pack.
3. You COULD GET PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or foam) as a back-up method of birth control until you have taken a white or green "active" pill every day for 7 days.

If you **MISS 2** white or green "active" pills in row in **THE 3rd WEEK:**
1. **If you are a Day-1 Starter:**
THROW OUT the rest of the pill pack and start a new pack that same day.
If you are a Sunday Starter:
Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month, but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You COULD GET PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or foam) as a back-up method of birth control until you have taken a white or green "active" pill every day for 7 days.

If you **MISS 3 OR MORE** white or green "active" pills in row (during the first 3 weeks):
1. **If you are a Day-1 Starter:**
THROW OUT the rest of the pill pack and start a new pack that same day.
If you are a Sunday Starter:
Keep taking 1 pill every day until Sunday. On Sunday, THROW OUT the rest of the pack and start a new pack of pills that same day.
2. You may not have your period this month, but this is expected. However, if you miss your period 2 months in a row, call your doctor or clinic because you might be pregnant.
3. You COULD GET PREGNANT if you have sex in the 7 days after you miss pills. You MUST use another birth control method (such as condoms or foam) as a back-up method of birth control until you have taken a white or green "active" pill every day for 7 days.

A REMINDER FOR THOSE ON 28-DAY PACKS:
IF YOU FORGET ANY OF THE 7 BROWN "REMINDER" PILLS IN WEEK 4:
THROW AWAY THE PILLS YOU MISSED.
KEEP TAKING 1 PILL EACH DAY UNTIL THE PACK IS EMPTY.
YOU DO NOT NEED A BACK-UP METHOD.

FINALLY, IF YOU ARE STILL NOT SURE WHAT TO DO ABOUT THE PILLS YOU HAVE MISSED:
Use a BACK-UP METHOD anytime you have sex.
KEEP TAKING ONE WHITE OR GREEN "ACTIVE" PILL EACH DAY until you can reach your doctor or clinic.

PREGNANCY DUE TO PILL FAILURE
The incidence of pill failure resulting in pregnancy is approximately 1% (ie, one pregnancy per 100 women per year) if taken every day as directed, but more typical failure rates are about 3%. If failure does occur, the risk to the fetus is minimal.

PREGNANCY AFTER STOPPING THE PILL
There may be some delay in becoming pregnant after you stop using oral contraceptives, especially if you had irregular menstrual cycles before you used oral contraceptives. It may be advisable to postpone conception until you begin menstruating regularly once you have stopped taking the pill and desire pregnancy.
There does not appear to be any increase in birth defects in newborn babies when pregnancy occurs soon after stopping the pill.

OVERDOSAGE
Serious ill effects have not been reported following ingestion of large doses of oral contraceptives by young children. Overdosage may cause nausea and withdrawal bleeding in females. In case of overdosage, contact your health care provider or pharmacist.

OTHER INFORMATION
Your health care provider will take a medical and family history and examine you before prescribing oral contraceptives. The physical examination may be delayed to another time if you request it and your health care provider believes that it is a good medical practice to postpone it. You should be reexamined at least once a year. Be sure to inform your health care provider if there is a family history of any of the conditions listed previously in this leaflet. Be sure to keep all appointments with your health care provider, because this is a time to determine if there are early signs of side effects of oral contraceptive use.
Do not use the drug for any condition other than the one for which it was prescribed. This drug has been prescribed specifically for you; do not give it to others who may want birth control pills.

HEALTH BENEFITS FROM ORAL CONTRACEPTIVES
In addition to preventing pregnancy, use of oral contraceptives may provide certain benefits. They are:
- Menstrual cycles may become more regular
- Blood flow during menstruation may be lighter and less iron may be lost. Therefore, anemia due to iron deficiency is less likely to occur
- Pain or other symptoms during menstruation may be encountered less frequently
- Ectopic (tubal) pregnancy may occur less frequently
- Noncancerous cysts or lumps in the breast may occur less frequently
- Acute pelvic inflammatory disease may occur less frequently
- Oral contraceptive use may provide some protection against developing two forms of cancer: cancer of the ovaries and cancer of the lining of the uterus.

If you want more information about birth control pills, ask your doctor or pharmacist. They have a more technical leaflet called the "Physician Insert," which you may wish to read.

Remembering to take tablets according to schedule is stressed because of its importance in providing you the greatest degree of protection.

MISSED MENSTRUAL PERIODS FOR BOTH DOSAGE REGIMENS
At times there may be no menstrual period after a cycle of pills. Therefore, if you miss one menstrual period but have taken the pills *exactly as you were supposed to*, continue as usual into the next cycle. If you have not taken the pills correctly and miss a menstrual period, *you may be pregnant* and should stop taking oral contraceptives until your doctor or health care provider determines whether or not you are pregnant. Until you can get to your doctor or health care provider, use another form of contraception. If two consecutive menstrual periods are missed, you should stop taking pills until it is determined whether or not you are pregnant. Although there does not appear to be any increase in birth defects in newborn babies, if you become pregnant while using oral contraceptives you should discuss the situation with your doctor or health care provider.

Periodic Examination
Your doctor or health care provider will take a complete medical and family history before prescribing oral contraceptives. At that time and about once a year thereafter, he or she will generally examine your blood pressure, breasts, abdomen, and pelvic organs (including a Papanicolaou smear, ie, test for cancer).

Keep this and all drugs out of the reach of children.
Rx only
Store below 30°C (86°F).
Revised November 1999

PARKE-DAVIS
Div of Warner-Lambert Co ©1997-'99
Morris Plains, NJ 07950 USA

Direct Medical Inquiries to:
Parke-Davis
Warner-Lambert Company
201 Tabor Road, Morris Plains, NJ 07950
Attn: Medical Affairs Department
0913G515

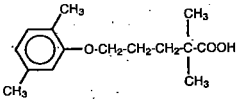
Shown in Product Identification Guide, page 330

LOPID®

[lō 'pid]
(Gemfibrozil Tablets, USP)

DESCRIPTION

LOPID® (gemfibrozil tablets, USP) is a lipid regulating agent. It is available as tablets for oral administration. Each tablet contains 600 mg gemfibrozil. Each also contains calcium stearate, NF; candelilla wax, FCC; microcrystalline cellulose, NF; hydroxypropyl cellulose, NF; hydroxypropylmethylcellulose, USP; methylparaben, NF; Opaspray white; polyethylene glycol, NF; polysorbate 80, NF; propylparaben, NF; colloidal silicon dioxide, NF; pregelatinized starch, NF. The chemical name is 5-(2,5-dimethylphenoxy)-2,2-dimethylpentanoic acid, with the following structural formula:



The empirical formula is $C_{15}H_{22}O_3$ and the molecular weight is 250.35; the solubility in water and acid is 0.0019% and in dilute base it is greater than 1%. The melting point is 58°–61° C. Gemfibrozil is a white solid which is stable under ordinary conditions.

CLINICAL PHARMACOLOGY

LOPID (gemfibrozil tablets, USP) is a lipid regulating agent which decreases serum triglycerides and very low density lipoprotein (VLDL) cholesterol, and increases high density lipoprotein (HDL) cholesterol. While modest decreases in total and low density lipoprotein (LDL) cholesterol may be observed with LOPID therapy, treatment of patients with elevated triglycerides due to Type IV hyperlipoproteinemia often results in a rise in LDL-cholesterol. LDL-cholesterol levels in Type IIb patients with elevations of both serum LDL-cholesterol and triglycerides are, in general, minimally affected by LOPID treatment; however, LOPID usually raises HDL-cholesterol significantly in this group. LOPID increases levels of high density lipoprotein (HDL) subfractions HDL_2 and HDL_3, as well as apolipoproteins AI and AII. Epidemiological studies have shown that both low HDL-cholesterol and high LDL-cholesterol are independent risk factors for coronary heart disease.
In the primary prevention component of the Helsinki Heart Study (refs. 1,2), in which 4081 male patients between the ages of 40 and 55 were studied in a randomized, double-blind, placebo-controlled fashion, LOPID therapy was associated with significant reductions in total plasma triglycerides and a significant increase in high density lipoprotein

cholesterol. Moderate reductions in total plasma cholesterol and low density lipoprotein cholesterol were observed for the LOPID treatment group as a whole, but the lipid response was heterogeneous, especially among different Fredrickson types. The study involved subjects with serum non-HDL-cholesterol of over 200 mg/dL and no previous history of coronary heart disease. Over the five-year study period, the LOPID group experienced a 1.4% absolute (34% relative) reduction in the rate of serious coronary events (sudden cardiac deaths plus fatal and nonfatal myocardial infarctions) compared to placebo, p=0.04 (see Table I). There was a 37% relative reduction in the rate of nonfatal myocardial infarction compared to placebo, equivalent to a treatment-related difference of 13.1 events per thousand persons. Deaths from any cause during the double-blind portion of the study totaled 44 (2.2%) in the LOPID randomization group and 43 (2.1%) in the placebo group.
[See table I at top right]
Among Fredrickson types, during the 5-year double-blind portion of the primary prevention component of the Helsinki Heart Study, the greatest reduction in the incidence of serious coronary events occurred in Type IIb patients who had elevations of both LDL-cholesterol and total plasma triglycerides. This subgroup of Type IIb gemfibrozil group patients had a lower mean HDL-cholesterol level at baseline than the Type IIa subgroup that had elevations of LDL-cholesterol and normal plasma triglycerides. The mean increase in HDL-cholesterol among the Type IIb patients in this study was 12.6% compared to placebo. The mean change in LDL-cholesterol among Type IIb patients was -4.1% with LOPID compared to a rise of 3.9% in the placebo subgroup. The Type IIb subjects in the Helsinki Heart Study had 26 fewer coronary events per thousand persons over five years in the gemfibrozil group compared to placebo. The difference in coronary events was substantially greater between LOPID and placebo for that subgroup of patients with the triad of LDL-cholesterol >175 mg/dL (>4.5 mmol), triglycerides >200 mg/dL (>2.2 mmol), and HDL-cholesterol <35 mg/dL (<0.90 mmol) (see Table I).
Further information is available from a 3.5 year (8.5 year cumulative) follow-up of all subjects who had participated in the Helsinki Heart Study. At the completion of the Helsinki Heart Study, subjects could choose to start, stop, or continue to receive LOPID; without knowledge of their own lipid values or double-blind treatment, 60% of patients originally randomized to placebo began therapy with LOPID and 60% of patients originally randomized to LOPID continued medication. After approximately 6.5 years following randomization, all patients were informed of their original treatment group and lipid values during the five years of the double-blind treatment. After further elective changes in LOPID treatment status, 61% of patients in the group originally randomized to LOPID were taking drug; in the group originally randomized to placebo, 65% were taking LOPID. The event rate per 1000 occurring during the open-label follow-up period is detailed in Table II.

Table II
Cardiac Events and All-Cause Mortality
(events per 1000 patients) Occurring During the 3.5 Year Open-Label Follow-up to the Helsinki Heart Study[1]

Group:	PDrop N=215	PN N=494	PL N=1283	LDrop N=221	LN N=574	LL N=1207
Cardiac Events	38.8	22.9	22.5	37.2	28.3	25.4
All-Cause Mortality	41.9	22.3	15.6	72.3	19.2	24.9

[1]The six open-label groups are designated first by the original randomization (P = placebo, L = Lopid) and then by the drug taken in the follow-up period (N = Attend clinic but took no drug, L = Lopid, Drop = No attendance at clinic during open-label).

Cumulative mortality through 8.5 years showed a 20% relative excess of deaths in the group originally randomized to LOPID versus the originally randomized placebo group and a 20% relative decrease in cardiac events in the group originally randomized to LOPID versus the originally randomized placebo group (see Table III). This analysis of the originally randomized "intent-to-treat" population neglects the possible complicating effects of treatment switching during the open-label phase. Adjustment of hazard ratios taking into account open-label treatment status from years 6.5 to 8.5 could change the reported hazard ratios for mortality toward unity.

Table III
Cardiac Events, Cardiac Deaths, Non-Cardiac Deaths and All-Cause Mortality in the Helsinki Heart Study, Years 0–8.5.[1]

Event	Lopid at Study Start	Placebo at Study Start	Lopid:Placebo Hazard Ratio[2]	CI Hazard Ratio[3]
Cardiac Events[4]	110	131	0.80	0.62–1.03
Cardiac Deaths	36	38	0.98	0.63–1.54
Non-Cardiac Deaths	65	45	1.40	0.95–2.05
All-Cause Mortality	101	83	1.20	0.90–1.61

[1] Intention-to-Treat Analysis of originally randomized patients neglecting the open-label treatment switches and exposure to study conditions.
[2] Hazard ratio for risk of event in the group originally randomized to Lopid compared to the group originally randomized to placebo neglecting open-label treatment switch and exposure to study condition.
[3] 95% confidence intervals of Lopid:placebo group hazard ratio.
[4] Fatal and non-fatal myocardial infarctions plus sudden cardiac deaths over the 8.5 year period.

It is not clear to what extent the findings of the primary prevention component of the Helsinki Heart Study can be extrapolated to other segments of the dyslipidemic population not studied (such as women, younger or older males, or those with lipid abnormalities limited solely to HDL-cholesterol) or to other lipid-altering drugs.
The secondary prevention component of the Helsinki Heart Study was conducted over five years in parallel and at the same centers in Finland in 628 middle-aged males excluded from the primary prevention component of the Helsinki Heart Study because of a history of angina, myocardial infarction or unexplained ECG changes (ref. 3). The primary efficacy endpoint of the study was cardiac events (the sum of fatal and non-fatal myocardial infarctions and sudden cardiac deaths). The hazard ratio (LOPID:placebo) for cardiac events was 1.47 (95% confidence limits 0.88–2.48, p=0.14). Of the 35 patients in the LOPID group who experienced cardiac events, 12 patients suffered events after discontinuation from the study. Of the 24 patients in the placebo group with cardiac events, 4 patients suffered events after discontinuation from the study. There were 17 cardiac deaths in the LOPID group and 8 in the placebo group (hazard ratio 2.18; 95% confidence limits 0.94–5.05, p=0.06). Ten of these deaths in the LOPID group and 3 in the placebo group occurred after discontinuation from therapy. In this study of patients with known or suspected coronary heart disease, no benefit from LOPID treatment was observed in reducing cardiac events or cardiac deaths. Thus, LOPID has shown benefit only in selected dyslipidemic patients without suspected or established coronary heart disease. Even in patients with coronary heart disease and the triad of elevated LDL-cholesterol, elevated triglycerides, plus low HDL-cholesterol, the possible effect of LOPID on coronary events has not been adequately studied.
No efficacy in the patients with established coronary heart disease was observed during the Coronary Drug Project with the chemically and pharmacologically related drug, clofibrate. The Coronary Drug Project was a 6-year randomized, double-blind study involving 1000 clofibrate, 1000 nicotinic acid, and 3000 placebo patients with known coronary heart disease. A clinically and statistically significant reduction in myocardial infarctions was seen in the concurrent nicotinic acid group compared to placebo; no reduction was seen with clofibrate.
The mechanism of action of gemfibrozil has not been definitely established. In man, LOPID has been shown to inhibit peripheral lipolysis and to decrease the hepatic extraction of free fatty acids, thus reducing hepatic triglyceride production. LOPID inhibits synthesis and increases clearance of VLDL carrier apolipoprotein B, leading to a decrease in VLDL production.
Animal studies suggest that gemfibrozil may, in addition to elevating HDL-cholesterol, reduce incorporation of long-chain fatty acids into newly formed triglycerides, accelerate turnover and removal of cholesterol from the liver, and increase excretion of cholesterol in the feces. LOPID is well absorbed from the gastrointestinal tract after oral administration. Peak plasma levels occur in 1 to 2 hours with a plasma half-life of 1.5 hours following multiple doses.
Gemfibrozil is completely absorbed after oral administration of LOPID tablets, reaching peak plasma concentrations 1 to 2 hours after dosing. Gemfibrozil pharmacokinetics are affected by the timing of meals relative to time of dosing. In one study (ref. 4), both the rate and extent of absorption of the drug were significantly increased when administered 0.5 hour before meals. Average AUC was reduced by 14–44% when LOPID was administered after meals compared to 0.5 hour before meals. In a subsequent study (ref. 4), rate of absorption of LOPID was maximum when administered 0.5 hour before meals with the Cmax 50–60% greater than when given either with meals or fasting. In this study, there were no significant effects on AUC of timing of dose relative to meals (see DOSAGE AND ADMINISTRATION).
LOPID mainly undergoes oxidation of a ring methyl group to successively form a hydroxymethyl and a carboxyl metabolite. Approximately seventy percent of the administered human dose is excreted in the urine, mostly as the glucuronide conjugate, with less than 2% excreted as unchanged gemfibrozil. Six percent of the dose is accounted for in the feces. Gemfibrozil is highly bound to plasma proteins and there is potential for displacement interactions with other drugs (see PRECAUTIONS).

INDICATIONS AND USAGE

LOPID (gemfibrozil tablets, USP) is indicated as adjunctive therapy to diet for:
1. Treatment of adult patients with very high elevations of serum triglyceride levels (Types IV and V hyperlipidemia) who present a risk of pancreatitis and who do not respond adequately to a determined dietary effort to control them. Patients who present such risk typically have serum triglycerides over 2000 mg/dL and have elevations of VLDL-cholesterol as well as fasting chylomicrons (Type V hyperlipidemia). Subjects who consistently have total serum or plasma triglycerides below 1000 mg/dL are unlikely to present a risk of pancreatitis. LOPID therapy may be considered for those subjects with triglyceride elevations between 1000 and 2000 mg/dL who have a history of pancreatitis or of recurrent abdominal pain typical of pancreatitis. It is recognized that some Type IV patients with triglycerides under 1000 mg/dL may, through dietary or alcoholic indiscretion, convert to a Type V pattern with massive triglyceride elevations accompanying fasting chylomicronemia, but the influence of LOPID therapy on the risk of pancreatitis in such situations has not been adequately studied. Drug therapy is not indicated for patients with Type I hyperlipoproteinemia, who have elevations of chylomicrons and plasma triglycerides, but who have normal levels of very low density lipoprotein (VLDL). Inspection of plasma refrigerated for 14 hours is helpful in distinguishing Types I, IV, and V hyperlipoproteinemia (ref. 5).
2. Reducing the risk of developing coronary heart disease only in Type IIb patients without history of or symptoms of existing coronary heart disease who have had an inadequate response to weight loss, dietary therapy, exercise, and other pharmacologic agents (such as bile acid sequestrants and nicotinic acid, known to reduce LDL- and raise HDL-cholesterol) and who have the following triad of lipid abnormalities: low HDL-cholesterol levels in addition to elevated LDL-cholesterol and elevated triglycerides (see WARNINGS, PRECAUTIONS, and CLINICAL PHARMACOLOGY). The National Cholesterol Education Program has defined a serum HDL-cholesterol value that is consistently below 35 mg/dL as constituting an independent risk factor for coronary heart disease (ref. 6). Patients with significantly elevated triglycerides should be closely observed when treated with gemfibrozil. In some patients with high triglyceride levels, treatment with gemfibrozil is associated with a significant increase in LDL-cholesterol. BECAUSE OF POTENTIAL TOXICITY SUCH AS MALIGNANCY, GALLBLADDER DISEASE, ABDOMINAL PAIN LEADING TO APPENDECTOMY AND OTHER ABDOMINAL SURGERIES, AN INCREASED INCIDENCE IN NON-CORONARY MORTALITY, AND THE 44% RELATIVE INCREASE DURING THE TRIAL PERIOD IN AGE-ADJUSTED ALL-CAUSE MORTALITY SEEN WITH THE CHEMICALLY AND PHARMACOLOGICALLY RELATED DRUG, CLOFIBRATE, THE POTENTIAL BENEFIT OF GEMFIBROZIL IN TREATING TYPE IIA PATIENTS WITH ELEVATIONS OF LDL-CHOLESTEROL ONLY IS NOT LIKELY TO OUTWEIGH THE RISKS. LOPID IS ALSO NOT INDICATED FOR THE TREATMENT OF PATIENTS WITH LOW HDL-CHOLESTEROL AS THEIR ONLY LIPID ABNORMALITY.

Continued on next page

This product information was prepared in August 2001. On these and other Parke-Davis Products, information may be obtained by addressing PARKE-DAVIS, a Warner-Lambert Division, a Pfizer Company, Morris Plains, New Jersey 07950.

Lopid—Cont.

In a subgroup analysis of patients in the Helsinki Heart Study with above-median HDL-cholesterol values at baseline (greater than 46.4 mg/dL), the incidence of serious coronary events was similar for gemfibrozil and placebo subgroups (see Table I).

The initial treatment for dyslipidemia is dietary therapy specific for the type of lipoprotein abnormality. Excess body weight and excess alcohol intake may be important factors in hypertriglyceridemia and should be managed prior to any drug therapy. Physical exercise can be an important ancillary measure, and has been associated with rises in HDL-cholesterol. Diseases contributory to hyperlipidemia such as hypothyroidism or diabetes mellitus should be looked for and adequately treated. Estrogen therapy is sometimes associated with massive rises in plasma triglycerides, especially in subjects with familial hypertriglyceridemia. In such cases, discontinuation of estrogen therapy may obviate the need for specific drug therapy of hypertriglyceridemia. The use of drugs should be considered only when reasonable attempts have been made to obtain satisfactory results with nondrug methods. If the decision is made to use drugs, the patient should be instructed that this does not reduce the importance of adhering to diet.

CONTRAINDICATIONS

1. Combination therapy of LOPID with cerivastatin due to the increased risk of myopathy and rhabdomyolysis (see WARNINGS).

2. Hepatic or severe renal dysfunction, including primary biliary cirrhosis.

3. Preexisting gallbladder disease (see WARNINGS).

4. Hypersensitivity to gemfibrozil.

WARNINGS

1. Because of chemical, pharmacological, and clinical similarities between gemfibrozil and clofibrate, the adverse findings with clofibrate in two large clinical studies may also apply to gemfibrozil. In the first of those studies, the Coronary Drug Project, 1000 subjects with previous myocardial infarction were treated for five years with clofibrate. There was no difference in mortality between the clofibrate-treated subjects and 3000 placebo-treated subjects, but twice as many clofibrate-treated subjects developed cholelithiasis and cholecystitis requiring surgery. In the other study, conducted by the World Health Organization (WHO), 5000 subjects without known coronary heart disease were treated with clofibrate for five years and followed one year beyond. There was a statistically significant, 44%, higher age-adjusted total mortality in the clofibrate-treated than in a comparable placebo-treated control group during the trial period. The excess mortality was due to a 33% increase in non-cardiovascular causes, including malignancy, post-cholecystectomy complications, and pancreatitis. The higher risk of clofibrate-treated subjects for gallbladder disease was confirmed.

Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality from any cause between the LOPID and placebo group is not statistically significantly different from the 29% excess mortality reported in the clofibrate group in the separate WHO study at the nine year follow-up (see CLINICAL PHARMACOLOGY). Noncoronary heart disease related mortality showed an excess in the group originally randomized to LOPID primarily due to cancer deaths observed during the open-label extension.

During the five year primary prevention component of the Helsinki Heart Study, mortality from any cause was 44 (2.2%) in the LOPID group and 43 (2.1%) in the placebo group; including the 3.5 year follow-up period since the trial was completed, cumulative mortality from any cause was 101 (4.9%) in the LOPID group and 83 (4.1%) in the group originally randomized to placebo (hazard ratio 1:20 in favor of placebo). Because of the more limited size of the Helsinki Heart Study, the observed difference in mortality from any cause between the LOPID and placebo groups at Year-5 or at Year-8.5 is not statistically significantly different from the 29% excess mortality reported in the clofibrate group in the separate WHO study at the nine year follow-up. Noncoronary heart disease related mortality showed an excess in the group originally randomized to LOPID at the 8.5 year follow-up (65 LOPID versus 45 placebo noncoronary deaths).

The incidence of cancer (excluding basal cell carcinoma) discovered during the trial and in the 3.5 years after the trial was completed was 51 (2.5%) in both originally randomized groups. In addition, there were 16 basal cell carcinomas in the group originally randomized to LOPID and 9 in the group randomized to placebo (p=0.22). There were 30 (1.5%) deaths attributed to cancer in the group originally randomized to LOPID and 18 (0.9%) in the group originally randomized to placebo (p=0.11). Adverse outcomes, including coronary events, were higher in gemfibrozil patients in a corresponding study in men with a history of known or suspected coronary heart disease in the secondary prevention component of the Helsinki Heart Study. (See CLINICAL PHARMACOLOGY.)

A comparative carcinogenicity study was also done in rats comparing three drugs in this class: fenofibrate (10 and 60 mg/kg; 0.3 and 1.6 times the human dose), clofibrate (400 mg/kg; 1.6 times the human dose), and gemfibrozil (250 mg/kg; 1.7 times the human dose). Pancreatic acinar adenomas were increased in males and females on fenofibrate; hepatocellular carcinoma and pancreatic acinar adenomas were increased in males and hepatic neoplastic nodules in females treated with clofibrate; hepatic neoplastic nodules were increased in males and females treated with clofibrate; hepatic neoplastic nodules were increased in males and females treated with gemfibrozil while testicular interstitial cell (Leydig cell) tumors were increased in males on all three drugs.

2. A gallstone prevalence substudy of 450 Helsinki Heart Study participants showed a trend toward a greater prevalence of gallstones during the study within the LOPID treatment group (7.5% vs 4.9% for the placebo group, a 55% excess for the gemfibrozil group). A trend toward a greater incidence of gallbladder surgery was observed for the LOPID group (17 vs 11 subjects, a 54% excess). This result did not differ statistically from the increased incidence of cholecystectomy observed in the WHO study in the group treated with clofibrate. Both clofibrate and gemfibrozil may increase cholesterol excretion into the bile leading to cholelithiasis. If cholelithiasis is suspected, gallbladder studies are indicated. LOPID therapy should be discontinued if gallstones are found.

3. Since a reduction of mortality from coronary heart disease has not been demonstrated and because liver and interstitial cell testicular tumors were increased in rats, LOPID should be administered only to those patients described in the INDICATIONS AND USAGE section. If a significant serum lipid response is not obtained, LOPID should be discontinued.

4. Concomitant Anticoagulants—Caution should be exercised when anticoagulants are given in conjunction with LOPID. The dosage of the anticoagulant should be reduced to maintain the prothrombin time at the desired level to prevent bleeding complications. Frequent prothrombin determinations are advisable until it has been definitely determined that the prothrombin level has stabilized.

5. Concomitant therapy with LOPID and an HMG-CoA reductase inhibitor is associated with an increased risk of skeletal muscle toxicity manifested as rhabdomyolysis, markedly elevated creatine kinase (CPK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure and death. **Because of an observed marked increased risk of myopathy and rhabdomyolysis, the specific combination of LOPID and cerivastatin is absolutely contraindicated (see CONTRAINDICATIONS).** IN PATIENTS WHO HAVE HAD AN UNSATISFACTORY LIPID RESPONSE TO EITHER DRUG ALONE, THE BENEFIT OF COMBINED THERAPY WITH LOPID AND HMG-CoA REDUCTASE INHIBITORS OTHER THAN CERIVASTATIN DOES NOT OUTWEIGH THE RISKS OF SEVERE MYOPATHY, RHABDOMYOLYSIS, AND ACUTE RENAL FAILURE (refs. 7, 8, 9, 10) (see Drug Interactions). The use of fibrates alone, including LOPID, may occasionally be associated with myositis. Patients receiving LOPID and complaining of muscle pain, tenderness or weakness should have prompt medical evaluation for myositis, including serum creatine-kinase level determination. If myositis is suspected or diagnosed, LOPID therapy should be withdrawn.

6. Cataracts—Subcapsular bilateral cataracts occurred in 10%, and unilateral in 6.3%, of male rats treated with gemfibrozil at 10 times the human dose.

	CAUSAL RELATIONSHIP PROBABLE	CAUSAL RELATIONSHIP NOT ESTABLISHED
General:		weight loss
Cardiac:		extrasystoles
Gastrointestinal:	cholestatic jaundice	pancreatitis hepatoma colitis
Central Nervous System:	dizziness somnolence paresthesia peripheral neuritis decreased libido depression headache	confusion convulsions syncope
Eye:	blurred vision	retinal edema
Genitourinary:	impotence	decreased male fertility renal dysfunction
Musculoskeletal:	myopathy myasthenia myalgia painful extremities arthralgia synovitis rhabdomyolysis (see WARNINGS and Drug Interactions under PRECAUTIONS)	
Clinical Laboratory:	increased creatine phosphokinase increased bilirubin increased liver transaminases (AST [SGOT], ALT [SGPT]) increased alkaline phosphatase	positive antinuclear antibody
Hematopoietic:	anemia leukopenia bone marrow hypoplasia eosinophilia	thrombocytopenia
Immunologic:	angioedema laryngeal edema urticaria	anaphylaxis Lupus-like syndrome vasculitis
Integumentary:	exfoliative dermatitis rash dermatitis pruritus	alopecia photosensitivity

PRECAUTIONS

1. **Initial Therapy**—Laboratory studies should be done to ascertain that the lipid levels are consistently abnormal. Before instituting LOPID therapy, every attempt should be made to control serum lipids with appropriate diet, exercise, weight loss in obese patients, and control of any medical problems such as diabetes mellitus and hypothyroidism that are contributing to the lipid abnormalities.

2. **Continued Therapy**—Periodic determination of serum lipids should be obtained, and the drug withdrawn if lipid response is inadequate after three months of therapy.

3. **Drug Interactions**—(A) **HMG-CoA reductase inhibitors:** The risk of myopathy and rhabdomyolysis is increased with combined gemfibrozil and HMG-CoA reductase inhibitor therapy (see CONTRAINDICATIONS). Myopathy or rhabdomyolysis with or without acute renal failure have been reported as early as three weeks after initiation of combined therapy or after several months (refs. 7, 8, 9, 10). (See WARNINGS.) There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

(B) **Anticoagulants:** CAUTION SHOULD BE EXERCISED WHEN ANTICOAGULANTS ARE GIVEN IN CONJUNCTION WITH LOPID. THE DOSAGE OF THE ANTICOAGULANT SHOULD BE REDUCED TO MAINTAIN THE PROTHROMBIN TIME AT THE DESIRED LEVEL TO PREVENT BLEEDING COMPLICATIONS. FREQUENT PROTHROMBIN DETERMINATIONS ARE ADVISABLE UNTIL IT HAS BEEN DEFINITELY DETERMINED THAT THE PROTHROMBIN LEVEL HAS STABILIZED.

4. **Carcinogenesis, Mutagenesis, Impairment of Fertility**—Long-term studies have been conducted in rats at 0.2 and 1.3 times the human exposure (based on AUC). The incidence of benign liver nodules and liver carcinomas was significantly increased in high dose male rats. The incidence of liver carcinomas increased also in low dose males, but this increase was not statistically significant (p=0.1). Male rats had a dose-related and statistically significant increase of benign Leydig cell tumors. The higher dose female rats had a significant increase in the combined incidence of benign and malignant liver neoplasms.

Long-term studies have been conducted in mice at 0.1 and 0.7 times the human exposure (based on AUC). There were no statistically significant differences from controls in the incidence of liver tumors, but the doses tested were lower than those shown to be carcinogenic with other fibrates.

Electron microscopy studies have demonstrated a florid hepatic peroxisome proliferation following LOPID administration to the male rat. An adequate study to test for peroxi-

some proliferation has not been done in humans but changes in peroxisome morphology have been observed. Peroxisome proliferation has been shown to occur in humans with either of two other drugs of the fibrate class when liver biopsies were compared before and after treatment in the same individual.

Administration of approximately 2 times the human dose (based on surface area) to male rats for 10 weeks resulted in a dose-related decrease of fertility. Subsequent studies demonstrated that this effect was reversed after a drug-free period of about eight weeks, and it was not transmitted to the offspring.

5. **Pregnancy Category C**—LOPID has been shown to produce adverse effects in rats and rabbits at doses between 0.5 and 3 times the human dose (based on surface area). There are no adequate and well-controlled studies in pregnant women. LOPID should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of LOPID to female rats at 2 times the human dose (based on surface area) before and throughout gestation caused a dose-related decrease in conception rate and an increase in stillborns and a slight reduction in pup weight during lactation. There were also dose-related increased skeletal variations. Anophthalmia occurred, but rarely.

Administration of 0.6 and 2 times the human dose (based on surface area) of LOPID to female rats from gestation day 15 through weaning caused dose-related decreases in birth weight and suppressions of pup growth during lactation.

Administration of 1 and 3 times the human dose (based on surface area) of LOPID to female rabbits during organogenesis caused a dose-related decrease in litter size and, at the high dose, an increased incidence of parietal bone variations.

6. **Nursing Mothers**—It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for LOPID in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

7. **Hematologic Changes**—Mild hemoglobin, hematocrit and white blood cell decreases have been observed in occasional patients following initiation of LOPID therapy. However, these levels stabilize during long-term administration. Rarely, severe anemia, leukopenia, thrombocytopenia, and bone marrow hypoplasia have been reported. Therefore, periodic blood counts are recommended during the first 12 months of LOPID administration.

8. **Liver Function**—Abnormal liver function tests have been observed occasionally during LOPID administration, including elevations of AST (SGOT), ALT (SGPT), LDH, bilirubin, and alkaline phosphatase. These are usually reversible when LOPID is discontinued. Therefore, periodic liver function studies are recommended and LOPID therapy should be terminated if abnormalities persist.

9. **Kidney Function**—There have been reports of worsening renal insufficiency upon the addition of LOPID therapy in individuals with baseline plasma creatinine >2.0 mg/dL. In such patients, the use of alternative therapy should be considered against the risks and benefits of a lower dose of LOPID.

10. **Pediatric Use**—Safety and efficacy in pediatric patients have not been established.

ADVERSE REACTIONS

In the double-blind controlled phase of the primary prevention component of the Helsinki Heart Study, 2046 patients received LOPID for up to five years. In that study, the following adverse reactions were statistically more frequent in subjects in the LOPID group:

	LOPID (N = 2046)	PLACEBO (N = 2035)
	Frequency in percent of subjects	
Gastrointestinal reactions	34.2	23.8
Dyspepsia	19.6	11.9
Abdominal pain	9.8	5.6
Acute appendicitis (histologically confirmed in most cases where data were available)	1.2	0.6
Atrial fibrillation	0.7	0.1

Adverse events reported by more than 1% of subjects, but without a significant difference between groups:

Diarrhea	7.2	6.5
Fatigue	3.8	3.5
Nausea/Vomiting	2.5	2.1
Eczema	1.9	1.2
Rash	1.7	1.3
Vertigo	1.5	1.3
Constipation	1.4	1.3
Headache	1.2	1.1

Gallbladder surgery was performed in 0.9% of LOPID and 0.5% of placebo subjects in the primary prevention component, a 64% excess, which is not statistically different from the excess of gallbladder surgery observed in the clofibrate compared to the placebo group of the WHO study. Gallbladder surgery was also performed more frequently in the LOPID group compared to placebo (1.9% vs 0.3%, p=0.07) in the secondary prevention component. A statistically significant increase in appendectomy in the gemfibrozil group was seen also in the secondary prevention component (6 on gemfibrozil vs 0 on placebo, p=0.014).

Nervous system and special senses adverse reactions were more common in the LOPID group. These included hypesthesia, paresthesias, and taste perversion. Other adverse reactions that were more common among LOPID treatment group subjects but where a causal relationship was not established include cataracts, peripheral vascular disease, and intracerebral hemorrhage.

From other studies it seems probable that LOPID is causally related to the occurrence of MUSCULOSKELETAL SYMPTOMS (see WARNINGS), and to ABNORMAL LIVER FUNCTION TESTS and HEMATOLOGIC CHANGES (see PRECAUTIONS).

Reports of viral and bacterial infections (common cold, cough, urinary tract infections) were more common in gemfibrozil treated patients in other controlled clinical trials of 805 patients. Additional adverse reactions that have been reported for gemfibrozil are listed below by system. These are categorized according to whether a causal relationship to treatment with LOPID is probable or not established:

[See table at top of previous page]

DOSAGE AND ADMINISTRATION

The recommended dose for adults is 1200 mg administered in two divided doses 30 minutes before the morning and evening meal (see CLINICAL PHARMACOLOGY).

OVERDOSAGE

There have been reported cases of overdosage with LOPID. In one case, a 7-year-old child recovered after ingesting up to 9 grams of LOPID. Symptoms reported with overdosage were abdominal cramps, abnormal liver function tests, diarrhea, increased CPK, joint and muscle pain, nausea and vomiting. Symptomatic supportive measures should be taken, should an overdose occur.

HOW SUPPLIED

LOPID (Tablet 737), white, elliptical, film-coated, scored tablets, each containing 600 mg gemfibrozil, are available as follows:

N 0071-0737-20: Bottles of 60
N 0071-0737-30: Bottles of 500
Parcode® No. 737

Store at controlled room temperature 20°–25°C (68°–77°F) [see USP]. Protect from light and humidity.

REFERENCES

1. Frick MH, Elo O, Haapa K, et al: Helsinki Heart Study: Primary prevention trial with gemfibrozil in middle-aged men with dyslipidemia. *N Engl J Med* 1987; 317:1237–1245.

2. Manninen V, Elo O, Frick MH, et al: Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. *JAMA* 1988; 260:641–651.

3. Frick MH, Heinonen OP, et al: Efficacy of gemfibrozil in dyslipidemic subjects with suspected heart disease. An ancillary study in the Helsinki Heart Study frame population. *Annals of Medicine* 1993; 25:41–45.

4. Data on file. Parke-Davis; Morris Plains, NJ.

5. Nikkila EA: Familial lipoprotein lipase deficiency and related disorders of chylomicron metabolism. In Stanbury JB et al. (eds.): *The Metabolic Basis of Inherited Disease*, 5th ed., McGraw-Hill, 1983, Chap. 30, pp. 622–642.

6. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol. *Arch Int Med* 1988;148:36–69.

7. Pierce LR, Wysowski DK, Gross TP. Myopathy and rhabdomyolysis associated with lovastatin/gemfibrozil combination therapy. JAMA 1990;264:71–75.

8. Bermingham RP, Whitsitt TB, Smart ML et al. Rhabdomyolysis in a patient receiving the combination of cerivastatin and gemfibrozil. Am J Health-Syst Pharm 2000;57: 461–464.

9. Duell PB, Connor WE, Illingworth DR. Rhabdomyolysis after taking atorvastatin with gemfibrozil. Am J Cardiol 1998;81:368–369.

10. Tal A, Rajeshawari M, Isley W. Rhabdomyolysis associated with simvastatin/gemfibrozil therapy. South Med J 1997;90:546–547.

Rx only

Revised July 2001

Manufactured by:
Parke Davis Pharmaceuticals, Ltd.
Vega Baja, PR 00694

Distributed by:
PARKE-DAVIS
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

69-5829-00-0

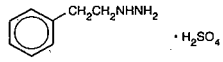
Shown in Product Identification Guide, page 330

NARDIL®

(Phenelzine Sulfate Tablets, USP)

DESCRIPTION

Nardil® (phenelzine sulfate) is a potent inhibitor of monoamine oxidase (MAO). Phenelzine sulfate is a hydrazine derivative. It is a molecular weight of 234.27 and is chemically described as $C_8H_{12}N_2 \cdot N_2SO_4$. Its chemical structure is shown below:



Molecular weight: 234.27

Each Nardil tablet for oral administration contains phenelzine sulfate equivalent to 15 mg of phenelzine base. Inactive ingredients include: acacia NF; calcium carbonate; carnauba wax, NF; corn-starch, NF; FD and C yellow No. 6; gelatin, NF; kaolin, USP; magnesium stearate, NF; mannitol, USP; pharmaceutical glaze, NF; povidone, USP; sucrose, NF; talc, USP; white wax, NF; white wheat flour.

CLINICAL PHARMACOLOGY

Monoamine oxidase is a complex enzyme system, widely distributed throughout the body. Drugs that inhibit monoamine oxidase in the laboratory are associated with a number of clinical effects. Thus, it is unknown whether MAO inhibition per se, other pharmacologic actions, or an interaction of both is responsible for the clinical effects observed. Therefore, the physician should become familiar with all the effects produced by drugs of this class.

INDICATIONS AND USAGE

Nardil has been found to be effective in depressed patients clinically characterized as "atypical," "nonendogenous," or "neurotic." These patients often have mixed anxiety and depression and phobic or hypochondriacal features. There is less conclusive evidence of its usefulness with severely depressed patients with endogenous features.

Nardil should rarely be the first antidepressant drug used. Rather, it is more suitable for use with patients who have failed to respond to the drugs more commonly used for these conditions.

CONTRAINDICATIONS

Nardil should not be used in patients who are hypersensitive to the drug or its ingredients, with pheochromocytoma, congestive heart failure, a history of liver disease, or abnormal liver function tests.

The potentiation of sympathomimetic substances and related compounds by MAO inhibitors may result in hypertensive crises (see WARNINGS). Therefore, patients being treated with Nardil should not take sympathomimetic drugs (including amphetamines, cocaine, methylphenidate, dopamine, epinephrine and norepinephrine) or related compounds (including methyldopa, L-dopa, L-tryptophan, L-tyrosine, and phenylalanine). Hypertensive crises during Nardil therapy may also be caused by the ingestion of foods with a high concentration of tyramine or dopamine. Therefore, patients being treated with Nardil should avoid high protein food that has undergone protein breakdown by aging, fermentation, pickling, smoking, or bacterial contamination. Patients should also avoid cheeses (especially aged varieties), pickled herring, beer, wine, liver, yeast extract (including brewer's yeast in large quantities), dry sausage (including Genoa salami, hard salami, pepperoni, and Lebanon bologna), pods of broad beans (fava beans), and yogurt. Excessive amounts of caffeine and chocolate may also cause hypertensive reactions.

Nardil should not be used in combination with dextromethorphan or with CNS depressants such as alcohol and certain narcotics. Excitation, seizures, delirium, hyperpyrexia, circulatory collapse, coma, and death have been reported in patients receiving MAOI therapy who have been given a single dose of meperidine. Nardil should not be administered together with or in rapid succession to other MAO inhibitors because HYPERTENSIVE CRISES and convulsive seizures, fever, marked sweating, excitation, delirium, tremor, coma, and circulatory collapse may occur.

A List of MAO Inhibitors by generic name follows:
pargyline hydrochloride
pargyline hydrochloride and methylclothiazide
furazolidone
isocarboxazid
procarbazine
tranylcypromine

Nardil should also not be used in combination with buspirone HCl, since several cases of elevated blood pressure have been reported in patients taking MAO inhibitors who were then given buspirone HCl. At least 10 days should elapse between the discontinuation of Nardil and the institution of another antidepressant or buspirone HCl, or the discontinuation of another MAO inhibitor and the institution of Nardil.

There have been reports of serious reactions (including hyperthermia, rigidity, myoclonic movements and death) when serotoninergic drugs (e.g., dexfenfluramine, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine) have been combined with an MAO inhibitor. Therefore the concomi-

Continued on next page

This product information was prepared in August 2001. On these and other Parke-Davis Products, information may be obtained by addressing PARKE-DAVIS, a Warner-Lambert Division, a Pfizer Company, Morris Plains, New Jersey 07950.

REDACTED

IN ITS

ENTIRETY